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Theory, Computation, and Modeling of Cancerous Systems

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THEORY, COMPUTATION, AND MODELING OF CANCEROUS SYSTEMS

by

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ABSTRACT

This dissertation focuses on three projects. In Chapter 1, we derive and implement the compact implicit integration factor method for numerically solving partial differential equations. In Chapters 2 and 3, we generalize and analyze a mathematical model for the nonlinear growth kinetics of breast cancer stem cells. And in Chapter 4, we develop a novel mathematical model for the HER2 signaling pathway to understand and predict breast cancer treatment.

Due to the high order spatial derivatives and stiff reactions, severe temporal stability constraints on the time step are generally required when developing numerical methods for solving high order partial differential equations. Implicit integration method (IIF) method along with its compact form (cIIF), which treats spatial derivatives exactly and reaction terms implicitly, provides excellent stability properties with good efficiency by decoupling the treatment of reaction and spatial derivatives. One major challenge for IIF is storage and calculation of the potential dense exponential matrices of the sparse discretization matrices resulted from the linear differential operators. The compact representation for IIF (cIIF) was introduced to save the computational cost and storage for this purpose. Another challenge is finding the matrix of high order space discretization, especially near the boundaries. In Chapter 1, we extend IIF method to high order discretization for spatial derivatives through an example of reaction diffusion equation with fourth order accuracy, while the computational cost and storage are similar to the general second order cIIF method. The method can also be efficiently applied to deal with other types of partial differential equations with both homogeneous and inhomogeneous boundary conditions. Direct

numerical simulations demonstrate the efficiency and accuracy of the approach.

Cancer stem cells are responsible for tumor survival and resurgence and are thus essential in developing novel therapeutic strategies against cancer. Mathematical models can help understand cancer stem and differentiated cell interaction in tumor growth, thus having the potential to aid in designing experiments to develop novel therapeutic strategies against cancer. In Chapter 2, by using theory of functional and ordinary differential equations, we study the existence and stability of non-linear growth kinetics of breast cancer stem cells. First we provide a sufficient condition for the existence and uniqueness of the solution for non-linear growth kinetics of breast cancer stem cells. Then we study the uniform asymptotic stability of the zero solution. By using linearization techniques, we also provide a criteria for uniform asymptotic stability of a non-trivial steady state solution with and without time delays. We present a theorem from complex analysis that gives certain conditions which allow for this criteria to be satisfied. Next we apply these theorems to a special case of the system of functional differential equations that has been used to model non-linear growth kinetics of breast cancer stem cells. The theoretical results are further justified by numerical testing examples. Consistent with the theories, our numerical examples show that the time delays can disrupt the stability. All the results can be easily extended to study more general cell lineage models.

Solid tumors are heterogeneous in composition. Cancer stem cells (CSCs) are a highly tumorigenic cell type found in developmentally diverse tumors that are believed to be resistant to standard chemotherapeutic drugs and responsible for tumor recurrence. Thus understanding the tumor growth kinetics is critical for developing novel strategies for cancer treatment. In Chapter 3, the moment stability of nonlinear stochastic systems of breast cancer stem cells with time-delays is investigated. First, based on the technique of the variation- of-constants formula, we obtain the second order moment equations for the nonlinear stochastic systems of breast cancer

stem cells with time-delays. By the comparison principle along with the established moment equations, we can get the comparative systems of the nonlinear stochastic systems of breast cancer stem cells with time-delays. Then moment stability theorems are established for the systems with the stability properties for the comparative systems. Based on the linear matrix inequality (LMI) technique, we next obtain a criteria for the exponential stability in mean square of the nonlinear stochastic systems for the dynamics of breast cancer stem cells with time-delays. Finally, some numerical examples are presented to illustrate the efficiency of the results.

Over-expression of human epidermal growth factor receptor 2 (HER2) plays a role in regulation of cancer stem cell (CSC) population in breast cancer. Current cancer therapy includes drugs that block HER2, however, patients can develop anti-HER2 drug resistance. Downstream of HER2 is nuclear factor κ B (NF κ B). The aberrant regulation of NF κ B leads to cancer growth, which makes it a promising target for cancer therapy, especially for those who have developed resistance to anti-HER2 treatment. In Chapter 4 we develop a novel mathematical model that represents the dynamics of the HER2 signaling pathway. By integrating experimental data with model simulations, we discover that interleukin-1 (IL1), which is downstream of HER2, is responsible for NF κ B activation. We perform global sensitivity analysis on the model to identify key reactions. Our modeling effort shows that IL1 is critical in NF κ B regulation, especially in the absence of HER2, making it a potential target in treating breast cancer for patients who have developed resistance to anti-HER2 drugs.

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CHAPTER 1

HIGH ORDER COMPACT INTEGRATION FACTOR METHOD

FOR SYSTEMS WITH INHOMOGENEOUS BOUNDARY

CONDITIONS

1.1 INTRODUCTION

Let Ω be an open rectangular domain in \mathbb{R}^d and a final time $T > 0$. In this paper, we consider solving a system of reaction-diffusion equation:

$$\begin{cases} \frac{\partial u}{\partial t} = -D\Delta u + f(u), & \mathbf{x} \in \Omega, t \in (0, T), \\ u|_{t=0} = u_0, & \mathbf{x} \in \Omega, \end{cases} \quad (1.1)$$

where $D > 0$ is the diffusion coefficient. Different boundary conditions such as the Dirichlet boundary condition, periodic boundary condition or Neumann boundary condition will all be studied in this paper. Due to severe time step constraints, one of the numerical difficulties to handle such equations is to efficiently solve the diffusion term Δu coupled with the stiff nonlinear reaction term $f(u)$. In general, the time step relies heavily on the stiffness of reactions and treatment of the high order derivatives. Integration factor (IF) or exponential differencing time (ETD) methods are popular methods for temporal partial differential equations (PDEs) [1–7].

To efficiently store and compute the exponential matrices in IIF for two and three dimensional systems in Cartesian coordinates with regular meshes, a class of compact implicit integration factor (cIIF) method [8] was introduced that has the same stability properties as the original IIF [9], but with significant improvement on storage and

computational savings for high spatial dimensions. In order to efficiently handle the complex domains with circular or spherical symmetry, cIIF methods were generalized to curvilinear coordinates through examples of polar and spherical coordinates [10]. One can also apply cIIF to stiff reactions and diffusions while using other specialized hyperbolic solvers (e.g WENO methods [11, 12]) for convection terms to solve reaction-diffusion-convection equations efficiently [13].

The compact form of integration factor method was often very hard to be directly applied to deal with problems involving cross derivatives. Recently in [14], the compact integration factor (cIF) method was applied to solve a family of semilinear fourth-order parabolic equations, in which the bi-Laplace operator is explicitly handled. The proposed method can also deal with not only stiff nonlinear reaction terms but also various types of homogeneous or inhomogeneous boundary conditions, while how to deal with inhomogeneous boundary conditions with cIF was not addressed before. Meanwhile, the IF method was designed and tested primarily for reaction-diffusion equations in previous studies. More recently in [15], cIF method was extended to solve the dissipative hydrodynamic equation system for incompressible fluid mixture flows with more complex mathematical structures. The IF strategy is applied after the system is discretized in space into a large differential and algebraic equation (DAE) system, which respects the total energy dissipation. The computational cost can be dramatically reduced through the use of discrete Fourier transform (DFT) by taking advantage of the circular structure of discretized matrices. The proposed approach has exhibited great numerical stability and energy dissipation property.

One challenge for integration factor (IF) method is to find the matrix of high order space discretization, especially near the boundaries, while all previous studies are mainly focusing on second order discretization in space. In this paper, we generalize IF methods for efficiently handling reaction-diffusion systems with high

order accuracy for various inhomogeneous boundary conditions. In this approach, we use standard fourth order central finite differences for spatial discretization coupled with compact implicit integration factor methods for time discretization. In two and three dimensional system, the discretized matrices arising from a compact representation of diffusion operator need to be diagonalized once and pre-calculated before each time step iteration. This new approach has similar stability properties as the general second order cIIF along with a similar computational cost. Thus the method is particularly suitable for high order partial differential equations in high dimensional systems with high order accuracy for both homogeneous and inhomogeneous boundary conditions.

To study the accuracy and efficiency, we first derive and implement the IF method to efficiently solve reaction-diffusion systems with inhomogeneous Neumann boundary conditions. Such approach can be similarly extended to all other inhomogeneous boundary conditions. The direct numerical simulations exhibit the excellent performance of the proposed approach through extensive numerical benchmark tests with the linear and nonlinear equations. The rest of the chapter is organized as follows. The derivation of the fourth order spatial discretization is in Section 1.2. The generalization of IF methods for reaction-diffusion systems for inhomogeneous Neumann boundary conditions are presented in Section 1.3, and numerical tests with linear and nonlinear cases are shown in Section 1.4. Finally a brief conclusion is drawn [16].

1.2 DERIVATION OF HIGH ORDER DISCRETIZATION

1.2.1 FOURTH ORDER CENTRAL FINITE DIFFERENCE DISCRETIZATION ON THE SECOND DERIVATIVE

Consider a function $u : \mathbb{R} \rightarrow \mathbb{R}$ that satisfies the reaction-diffusion equation

$$\frac{\partial \mathbf{u}}{\partial t} = D \frac{\partial^2 \mathbf{u}}{\partial x^2} + \mathbf{F}(\mathbf{u}), \quad a < x < b. \quad (1.2)$$

After spatial discretization, this equation can be written as

$$\frac{d\mathbf{U}}{dt} = \mathbf{A}\mathbf{U} + \mathcal{F}(\mathbf{U}), \quad (1.3)$$

where $\mathbf{U} \in \mathbb{R}^{(N+1) \times 1}$, $\mathbf{A} \in \mathbb{R}^{(N+1) \times (N+1)}$, and \mathcal{F} defined as above. We will derive a fourth order central finite difference discretization on the second derivative, which will tell us the form of \mathbf{A} .

Let (a, b) be an interval and $a = x_0 < x_1 < \dots < x_N = b$ be a partition with step size $h = (b - a)/N$. Then we have the following Taylor series expansions.

$$\begin{aligned} u(x_i + h) &= u(x_i) + \frac{u'(x_i)}{1!}(h) + \frac{u''(x_i)}{2!}(h)^2 + \frac{u'''(x_i)}{3!}(h)^3 + \frac{u^{(4)}(x_i)}{4!}(h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(h)^5 + O(h^6) \end{aligned} \quad (1.4)$$

$$\begin{aligned} u(x_i - h) &= u(x_i) + \frac{u'(x_i)}{1!}(-h) + \frac{u''(x_i)}{2!}(-h)^2 + \frac{u'''(x_i)}{3!}(-h)^3 + \frac{u^{(4)}(x_i)}{4!}(-h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(-h)^5 + O(h^6) \end{aligned} \quad (1.5)$$

$$\begin{aligned} u(x_i + 2h) &= u(x_i) + \frac{u'(x_i)}{1!}(2h) + \frac{u''(x_i)}{2!}(2h)^2 + \frac{u'''(x_i)}{3!}(2h)^3 + \frac{u^{(4)}(x_i)}{4!}(2h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(2h)^5 + O(h^6) \end{aligned} \quad (1.6)$$

$$\begin{aligned} u(x_i - 2h) &= u(x_i) + \frac{u'(x_i)}{1!}(-2h) + \frac{u''(x_i)}{2!}(-2h)^2 + \frac{u'''(x_i)}{3!}(-2h)^3 + \frac{u^{(4)}(x_i)}{4!}(-2h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(-2h)^5 + O(h^6) \end{aligned} \quad (1.7)$$

$$\begin{aligned} u(x_i + 3h) &= u(x_i) + \frac{u'(x_i)}{1!}(3h) + \frac{u''(x_i)}{2!}(3h)^2 + \frac{u'''(x_i)}{3!}(3h)^3 + \frac{u^{(4)}(x_i)}{4!}(3h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(3h)^5 + O(h^6) \end{aligned} \quad (1.8)$$

$$\begin{aligned} u(x_i - 3h) &= u(x_i) + \frac{u'(x_i)}{1!}(-3h) + \frac{u''(x_i)}{2!}(-3h)^2 + \frac{u'''(x_i)}{3!}(-3h)^3 + \frac{u^{(4)}(x_i)}{4!}(-3h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(-3h)^5 + O(h^6) \end{aligned} \quad (1.9)$$

$$\begin{aligned} u(x_i + 4h) &= u(x_i) + \frac{u'(x_i)}{1!}(4h) + \frac{u''(x_i)}{2!}(4h)^2 + \frac{u'''(x_i)}{3!}(4h)^3 + \frac{u^{(4)}(x_i)}{4!}(4h)^4 \\ &\quad + \frac{u^{(5)}(x_i)}{5!}(4h)^5 + O(h^6) \end{aligned} \quad (1.10)$$

$$\begin{aligned}
u(x_i - 4h) = & u(x_i) + \frac{u'(x_i)}{1!}(-4h) + \frac{u''(x_i)}{2!}(-4h)^2 + \frac{u'''(x_i)}{3!}(-4h)^3 + \frac{u^{(4)}(x_i)}{4!}(-4h)^4 \\
& + \frac{u^{(5)}(x_i)}{5!}(-4h)^5 + O(h^6)
\end{aligned} \tag{1.11}$$

Denote $u_i = u(x_i)$, $u_{i+1} = u(x_i + h)$, etc. Rearranging these equations and then adding (1.6) to (1.7) yields

$$u_{i+2} - 2u_i + u_{i-2} = 4u_i''h^2 + \frac{4}{3}u_i^{(4)}h^4 + O(h^6). \tag{1.12}$$

Similarly, from (1.4) and (1.5) we have

$$u_{i+1} - 2u_i + u_{i-1} = u_i''h^2 + \frac{1}{12}u_i^{(4)}h^4 + O(h^6). \tag{1.13}$$

Subtracting $16 \cdot (1.13)$ from (1.12) yields

$$u_{i+2} - 16u_{i+1} + 30u_i - 16u_{i-1} + u_{i-2} = -12u_i''h^2 + O(h^6). \tag{1.14}$$

By rearranging this equation we get a fourth order approximation for the second derivative:

$$u_i'' \approx \frac{-u_{i+2} + 16u_{i+1} - 30u_i + 16u_{i-1} - u_{i-2}}{12h^2}. \tag{1.15}$$

Another way to get the same fourth order approximation for the second derivative is to increase the step size in (1.13) from h to $2h$.

$$\begin{aligned}
u_{i+2} - 2u_i + u_{i-2} &= u_i''(2h)^2 + \frac{1}{12}u_i^{(4)}(2h)^4 + O(h^6) \\
&= 4u_i''h^2 + \frac{4}{3}u_i^{(4)}h^4 + O(h^6)
\end{aligned} \tag{1.16}$$

Again subtracting $16 \cdot (1.13)$ from (1.16) yields

$$u_{i+2} - 16u_{i+1} + 30u_i - 16u_{i-1} + u_{i-2} = -12u_i''h^2 + O(h^6), \tag{1.17}$$

from which we get

$$u_i'' \approx \frac{-u_{i+2} + 16u_{i+1} - 30u_i + 16u_{i-1} - u_{i-2}}{12h^2}. \tag{1.18}$$

This tells us the the form of \mathbf{A} , excluding the first and last two rows. They will be determined by the boundary condition. Let $\tilde{\mathbf{A}} \in \mathbf{R}^{(N-3) \times (N+1)}$ denote the interior rows of \mathbf{A} . Then

$$\tilde{\mathbf{A}} = \frac{D}{12h^2} \times \begin{pmatrix} -1 & 16 & -30 & 16 & -1 & & \\ & -1 & 16 & -30 & 16 & -1 & \\ & & \ddots & \ddots & \ddots & \ddots & \ddots \\ & & & -1 & 16 & -30 & 16 & -1 \end{pmatrix}_{(N-3) \times (N+1)} \quad (1.19)$$

1.2.2 BOUNDARY-VALUE EQUATIONS

Note that for $i = 0, 1$, the scheme (1.15) contains the points u_{-1} and u_{-2} , and for $i = N - 1, N$, it contains the points u_{N+1} and u_{N+2} . In this section we will derive a fourth order approximation for these points again from the Taylor series.

Neumann Boundary Condition

Consider the nonhomogeneous Neumann boundary condition

$$\frac{\partial u}{\partial x}(a) = \alpha, \quad \frac{\partial u}{\partial x}(b) = \beta. \quad (1.20)$$

Subtracting (1.5) from (1.4) and (1.7) from (1.6) yields

$$u_{i+1} - u_{i-1} = 2u'_i h + \frac{u''_i}{3} h^3 + O(h^5) \quad (1.21)$$

$$u_{i+2} - u_{i-2} = 4u'_i h + \frac{8u''_i}{3} h^3 + O(h^5). \quad (1.22)$$

Subtracting (1.22) from 8·(1.21) and rearranging yields a fourth order approximation for the first derivative:

$$u'_i \approx \frac{-u_{i+2} + 8u_{i+1} - 8u_{i-1} + u_{i-2}}{12h}. \quad (1.23)$$

We will derive another fourth order approximation for the first derivative, this time by including the points u_{i+3} and u_{i+4} instead of u_{i-2} .

From the operations $4 \cdot (1.8) - 9 \cdot (1.6)$ and $(1.10) - 4 \cdot (1.6)$, we get

$$4u_{i+3} - 9u_{i+2} = -5u_i - 6u'_i h + 6u'''_i h^3 + \frac{15u^{(4)}_i}{2} h^4 + O(h^5) \quad (1.24)$$

$$u_{i+4} - 4u_{i+2} = -3u_i - 4u'_i h + \frac{16u'''_i}{3} h^3 + 8u^{(4)}_i h^4 + O(h^5). \quad (1.25)$$

$15 \cdot (1.25) - 16 \cdot (1.24)$ yields

$$15u_{i+4} - 64u_{i+3} + 84u_{i+2} - 35u_i = 36u'_i h - 16u'''_i h^3 + O(h^5). \quad (1.26)$$

Now, $(1.26) + 48 \cdot (1.21)$ yields

$$15u_{i+4} - 64u_{i+3} + 84u_{i+2} + 48u_{i+1} - 35u_i - 48u_{i-1} = 132u'_i h + O(h^5), \quad (1.27)$$

from which we get another fourth order approximation for the first derivative:

$$u'_i \approx \frac{15u_{i+4} - 64u_{i+3} + 84u_{i+2} + 48u_{i+1} - 35u_i - 48u_{i-1}}{132h}. \quad (1.28)$$

From (1.20) we have the boundary value $u'_0 = \alpha$. Then for $i = 0$, (1.28) becomes

$$15u_4 - 64u_3 + 84u_2 + 48u_1 - 35u_0 - 48u_{-1} = 132h\alpha, \quad (1.29)$$

from which we get

$$u_{-1} = \frac{15u_4 - 64u_3 + 84u_2 + 48u_1 - 35u_0}{48} - \frac{11h}{4}\alpha. \quad (1.30)$$

Likewise, (1.23) becomes

$$-u_2 + 8u_1 - 8u_{-1} + u_{-2} = 12h\alpha, \quad (1.31)$$

from which we get

$$\begin{aligned} u_{-2} &= u_2 - 8u_1 + 8u_{-1} + 12h\alpha \\ &= u_2 - 8u_1 + 8 \left(\frac{15u_4 - 64u_3 + 84u_2 + 48u_1 - 35u_0}{48} - \frac{11h}{4}\alpha \right) + 12h\alpha \\ &= \frac{15u_4 - 64u_3 + 90u_2 - 35u_0}{6} - 10h\alpha. \end{aligned} \quad (1.32)$$

Substituting (1.30) and (1.32) into (1.15) for $i = 0, 1$ yields

$$\begin{aligned} u_0'' &= \frac{\frac{5}{2}u_4 - \frac{32}{3}u_3 + 12u_2 + 32u_1 - \frac{215}{6}u_0}{12h^2} - \frac{34h\alpha}{12h^2} \\ u_1'' &= \frac{-\frac{5}{16}u_4 + \frac{1}{3}u_3 + \frac{57}{4}u_2 - 31u_1 + \frac{803}{48}u_0}{12h^2} + \frac{\frac{11h}{4}\alpha}{12h^2}. \end{aligned} \quad (1.33)$$

For the homogeneous Neumann boundary condition, we get the same result, but without the α term.

We will derive another fourth order approximation for the first derivative, this time by including the points u_{i-3} and u_{i-4} instead of u_{i+2} .

From the operations $4 \cdot (1.9) - 9 \cdot (1.7)$ and $(1.11) - 4 \cdot (1.7)$, we get

$$4u_{i-3} - 9u_{i-2} = -5u_i + 6u_i'h - 6u_i'''h^3 + \frac{15u_i^{(4)}}{2}h^4 + O(h^5) \quad (1.34)$$

$$u_{i-4} - 4u_{i-2} = -3u_i + 4u_i'h - \frac{16u_i'''}{3}h^3 + 8u_i^{(4)}h^4 + O(h^5). \quad (1.35)$$

$15 \cdot (1.35) - 16 \cdot (1.34)$ yields

$$15u_{i-4} - 64u_{i-3} + 84u_{i-2} - 35u_i = -36u_i'h + 16u_i'''h^3 + O(h^5). \quad (1.36)$$

Now, $(1.36) - 48 \cdot (1.21)$ yields

$$15u_{i-4} - 64u_{i-3} + 84u_{i-2} - 48u_{i+1} - 35u_i + 48u_{i-1} = -132u_i'h + O(h^5), \quad (1.37)$$

from which we get another fourth order approximation for the first derivative:

$$u_i' \approx \frac{-15u_{i-4} + 64u_{i-3} - 84u_{i-2} + 48u_{i+1} + 35u_i - 48u_{i-1}}{132h}. \quad (1.38)$$

From (1.20) we have the boundary value $u_N' = \beta$. Then for $i = N$, (1.38) becomes

$$-15u_{N-4} + 64u_{N-3} - 84u_{N-2} + 48u_{N+1} + 35u_N - 48u_{N-1} = 132h\beta, \quad (1.39)$$

from which we get

$$u_{N+1} = \frac{15u_{N-4} - 64u_{N-3} + 84u_{N-2} + 48u_{N-1} - 35u_N}{48} + \frac{11h}{4}\beta. \quad (1.40)$$

Likewise, (1.23) becomes

$$-u_{N+2} + 8u_{N+1} - 8u_{N-1} + u_{N-2} = 12h\beta, \quad (1.41)$$

from which we get

$$\begin{aligned} u_{N+2} &= u_{N-2} - 8u_{N-1} + 8u_{N+1} - 12h\beta \\ &= u_{N-2} - 8u_{N-1} + 8 \left(\frac{15u_{N-4} - 64u_{N-3} + 84u_{N-2} + 48u_{N-1} - 35u_N}{48} + \frac{11h}{4}\beta \right) \\ &\quad - 12h\beta \\ &= \frac{15u_{N-4} - 64u_{N-3} + 90u_{N-2} - 35u_N}{6} + 10h\beta. \end{aligned} \quad (1.42)$$

Substituting (1.40) and (1.42) into (1.15) for $i = N - 1, N$ yields

$$\begin{aligned} u_{N-1} &= \frac{\frac{803}{48}u_N - 31u_{N-1} + \frac{57}{4}u_{N-2} + \frac{1}{3}u_{N-3} - \frac{5}{16}u_{N-4}}{12h^2} - \frac{\frac{11h}{4}\beta}{12h^2} \\ u_N &= \frac{-\frac{215}{6}u_N + 32u_{N-1} + 12u_{N-2} - \frac{32}{3}u_{N-3} + \frac{5}{2}u_{N-4}}{12h^2} + \frac{34h\beta}{12h^2}. \end{aligned} \quad (1.43)$$

For the homogeneous Neumann boundary condition, we get the same result, but without the β term.

The α and β terms in (1.33) and (1.43) can be moved to the reaction term in (1.3). Incorporating these equations in $\tilde{\mathbf{A}}$ yields

$$\mathbf{A} = \frac{D}{12h^2} \times \begin{pmatrix} -\frac{215}{6} & 32 & 12 & -\frac{32}{3} & \frac{5}{2} & & & & \\ \frac{803}{48} & -31 & \frac{57}{4} & \frac{1}{3} & -\frac{5}{16} & & & & \\ -1 & 16 & -30 & 16 & -1 & & & & \\ & -1 & 16 & -30 & 16 & -1 & & & \\ & & \ddots & \ddots & \ddots & \ddots & \ddots & & \\ & & & -1 & 16 & -30 & 16 & -1 & \\ & & & & -1 & 16 & -30 & 16 & -1 \\ & & & & -\frac{5}{16} & \frac{1}{3} & \frac{57}{4} & -31 & \frac{803}{48} \\ & & & & \frac{5}{2} & -\frac{32}{3} & 12 & 32 & -\frac{215}{6} \end{pmatrix}_{(N+1) \times (N+1)}. \quad (1.44)$$

Dirchlet Boundary Condition

Consider the inhomogeneous Dirchlet boundary condition

$$u(a) = \alpha, \quad u(b) = \beta. \quad (1.45)$$

Since we know u_0 and u_N , we do not need rows 0 and N in \mathbf{A} . We still need to rewrite the expressions for u_1 and u_{N-1} , though, since they involve the terms u_{-1} and u_{N+1} , respectively.

Recall the fourth order approximations derived for the first derivative of u in the previous section

$$\begin{aligned} u'_i &\approx \frac{-u_{i+2} + 8u_{i+1} - 8u_{i-1} + u_{i-2}}{12h}, \\ u'_i &\approx \frac{15u_{i+4} - 64u_{i+3} + 84u_{i+2} + 48u_{i+1} - 35u_i - 48u_{i-1}}{132h}, \\ u'_i &\approx \frac{-15u_{i-4} + 64u_{i-3} - 84u_{i-2} + 48u_{i+1} + 35u_i - 48u_{i-1}}{132h}. \end{aligned}$$

Subtracting the top equation from the middle equation yields

$$0 = 15u_{i+4} - 64u_{i+3} + 95u_{i+2} - 40u_{i+1} - 35u_i + 40u_{i-1} - 11u_{i-2} \quad (1.46)$$

From taking $i = 1$ and rearranging, we get

$$u_{-1} = \frac{1}{11}(15u_5 - 64u_4 + 95u_3 - 40u_2 - 35u_1 + 40u_0). \quad (1.47)$$

Subtracting the bottom equation from the top equation yields

$$0 = -11u_{i+2} + 40u_{i+1} - 35u_i - 40u_{i-1} + 95u_{i-2} - 64u_{i-3} + 15u_{i-4} \quad (1.48)$$

From taking $i = N - 1$ and rearranging, we get

$$u_{N+1} = \frac{1}{11}(40u_N - 35u_{N-1} - 40u_{N-2} + 95u_{N-3} - 64u_{N-4} + 15u_{N-5}) \quad (1.49)$$

Substituting (1.47) and (1.49) into (1.15) for $i = 1, N - 1$ yields

$$\begin{aligned}
u_1 &= \frac{-\frac{15}{11}u_5 + \frac{64}{11}u_4 - \frac{106}{11}u_3 + \frac{216}{11}u_2 - \frac{295}{11}u_1 + \frac{136}{11}u_0}{12h^2} \\
&= \frac{-\frac{15}{11}u_5 + \frac{64}{11}u_4 - \frac{106}{11}u_3 + \frac{216}{11}u_2 - \frac{295}{11}u_1}{12h^2} + \frac{\frac{136}{11}\alpha}{12h^2} \\
u_{N-1} &= \frac{\frac{136}{11}u_N - \frac{295}{11}u_{N-1} + \frac{216}{11}u_{N-2} - \frac{106}{11}u_{N-3} + \frac{64}{11}u_{N-4} - \frac{15}{11}u_{N-5}}{12h^2} \\
&= \frac{-\frac{295}{11}u_{N-1} + \frac{216}{11}u_{N-2} - \frac{106}{11}u_{N-3} + \frac{64}{11}u_{N-4} - \frac{15}{11}u_{N-5}}{12h^2} + \frac{\frac{136}{11}\beta}{12h^2}. \tag{1.50}
\end{aligned}$$

For the homogeneous Dirichlet boundary condition, we get the same result, but without the α and β terms.

The α and β terms in (1.50) can be moved to the reaction term in (1.3). Incorporating these equations in $\tilde{\mathbf{A}}$ yields

$$\mathbf{A} = \frac{D}{12h^2} \times \begin{pmatrix} -\frac{295}{11} & \frac{216}{11} & -\frac{106}{11} & \frac{64}{11} & -\frac{15}{11} & & & & \\ 16 & -30 & 16 & -1 & 0 & & & & \\ -1 & 16 & -30 & 16 & -1 & & & & \\ & -1 & 16 & -30 & 16 & -1 & & & \\ & & \ddots & \ddots & \ddots & \ddots & \ddots & & \\ & & & -1 & 16 & -30 & 16 & -1 & \\ & & & & -1 & 16 & -30 & 16 & -1 \\ & & & & 0 & -1 & 16 & -30 & 16 \\ & & & & & -\frac{15}{11} & \frac{64}{11} & -\frac{106}{11} & \frac{216}{11} & -\frac{295}{11} \end{pmatrix}_{(N-1) \times (N-1)}. \tag{1.51}$$

1.2.3 DEALING WITH THE EXTRA TERM FROM THE INHOMOGENEOUS NEUMANN BOUNDARY CONDITION

With the inhomogeneous Neumann boundary condition, we get extra terms for u_0 , u_1 , u_{N-1} , and u_N from (1.33) and (1.43). Define

$$\mathcal{G}(t) = \frac{D}{h} \times \begin{pmatrix} -\frac{17\alpha(t)}{6} \\ \frac{11\alpha(t)}{48} \\ 0 \\ \vdots \\ 0 \\ -\frac{11\beta(t)}{48} \\ \frac{17\beta(t)}{6} \end{pmatrix}_{(N+1) \times 1}. \quad (1.52)$$

Likewise, with the inhomogeneous Dirchlet boundary condition, we get extra terms for u_1 , u_2 , u_{N-2} , and u_{N-1} from (1.50) and (1.15). Define

$$\mathcal{G}(t) = \frac{D}{h^2} \times \begin{pmatrix} \frac{34\alpha(t)}{33} \\ -\frac{\alpha(t)}{12} \\ 0 \\ \vdots \\ 0 \\ -\frac{\beta(t)}{12} \\ \frac{34\beta(t)}{33} \end{pmatrix}_{(N-1) \times 1}. \quad (1.53)$$

Then (1.3) becomes

$$\frac{d\mathbf{U}}{dt} = \mathbf{A}\mathbf{U} + \mathcal{F}(\mathbf{U}) + \mathcal{G}. \quad (1.54)$$

1.3 HIGH ORDER INTEGRATION FACTOR (IF) METHOD WITH INHOMOGENEOUS BOUNDARY CONDITIONS

1.3.1 ONE-DIMENSION

First we consider a one-dimensional reaction-diffusion equation with inhomogeneous Neumann boundary condition,

$$\begin{cases} \frac{\partial \mathbf{u}}{\partial t} = D \frac{\partial^2 \mathbf{u}}{\partial x^2} + \mathbf{F}(\mathbf{u}), & x \in \Omega, \quad t \in [0, T] \\ \frac{\partial \mathbf{u}}{\partial x}(t, x) = g(t, x) & x \in \partial\Omega, \quad t \in [0, T] \end{cases}, \quad (1.55)$$

where $\Omega = [a, b]$. We first discretize the spatial domain by the mesh: $x_i = a + i \times h$ where $h = (b - a)/N$ and $0 \leq i \leq N$. Using the fourth order central difference discretization on the diffusion, we obtain a system of nonlinear ODEs

$$\frac{du_i}{dt} = D \left(\frac{-u_{i+2} + 16u_{i+1} - 30u_i + 16u_{i-1} - u_{i-2}}{12h^2} \right) + \mathbf{F}(u_i) + \mathbf{G}. \quad (1.56)$$

Next we define vectors \mathbf{U} and \mathcal{G} and a matrix \mathbf{A} by

$$\mathbf{U} = (u_0 \quad \cdots \quad u_i \quad \cdots \quad u_N)_{(N+1) \times 1}^T, \quad (1.57)$$

$$\mathcal{G} = \frac{D}{h^2} \times \begin{pmatrix} -\frac{17g(t, x_0)}{6} \\ \frac{11g(t, x_0)}{48} \\ 0 \\ \vdots \\ 0 \\ -\frac{11g(t, x_N)}{48} \\ \frac{17g(t, x_N)}{6} \end{pmatrix}_{(N+1) \times 1}, \quad (1.58)$$

and

$$\mathbf{A} = \frac{D}{12h^2} \times \begin{pmatrix} -\frac{215}{6} & 32 & 12 & -\frac{32}{3} & \frac{5}{2} & & & & \\ \frac{803}{48} & -31 & \frac{57}{4} & \frac{1}{3} & -\frac{5}{16} & & & & \\ -1 & 16 & -30 & 16 & -1 & & & & \\ & -1 & 16 & -30 & 16 & -1 & & & \\ & & \ddots & \ddots & \ddots & \ddots & \ddots & & \\ & & & -1 & 16 & -30 & 16 & -1 & \\ & & & -\frac{5}{16} & \frac{1}{3} & \frac{57}{4} & -31 & \frac{803}{48} & \\ & & & \frac{5}{2} & -\frac{32}{3} & 12 & 32 & -\frac{215}{6} & \end{pmatrix}_{(N+1) \times (N+1)} \quad (1.59)$$

In terms of this vector and matrix, the semi-discretized form (1.56) becomes

$$\frac{d\mathbf{U}}{dt} = \mathbf{A}\mathbf{U} + \mathcal{F}(\mathbf{U}) + \mathcal{G}. \quad (1.60)$$

To apply the integration factor technique to the compact discretization form (1.60), we multiply (1.60) by exponential matrix $e^{-\mathbf{A}t}$ from the left to obtain

$$\frac{d(e^{-\mathbf{A}t}\mathbf{U})}{dt} = e^{-\mathbf{A}t}\mathcal{F}(\mathbf{U}) + e^{-\mathbf{A}t}\mathcal{G}. \quad (1.61)$$

Integration of (1.61) over one time step from t_n to $t_{n+1} \equiv t_n + \Delta t$, where Δt is the time step, leads to

$$\mathbf{U}_{n+1} = e^{\mathbf{A}\Delta t}\mathbf{U}_n + e^{\mathbf{A}\Delta t} \left(\int_0^{\Delta t} e^{-\mathbf{A}\tau} \mathcal{F}(\mathbf{U}(t_n + \tau)) d\tau + \int_0^{\Delta t} e^{-\mathbf{A}\tau} \mathcal{G}(t_n + \tau) d\tau \right). \quad (1.62)$$

As discussed in [14, 17], to evaluate the integral resulted from the inhomogeneous boundary terms

$$\int_0^{\Delta t} e^{-\mathbf{A}\tau} \mathcal{G}(t_n + \tau) d\tau,$$

we need to be careful since $\mathcal{G}(t_n + \tau)$ contains entries which decay with highly different speeds along the time, and it involves the factors of $1/h^2$ which could quickly amplify errors arising from the time discretization, which would cause severe numerical

instability. To overcome this difficulty, we will apply an elegant approach proposed in [14, 17], which will be described with details in the following.

To construct a scheme of r th order truncation error, we approximate the integrands in (1.62),

$$\mathcal{H}_1(\tau) \equiv e^{-\mathbf{A}\tau} \mathcal{F}(\mathbf{U}(t_n + \tau)), \quad \mathcal{H}_2(\tau) \equiv \mathcal{G}(t_n + \tau),$$

using a $(r-1)$ th order Lagrange polynomial at a set of interpolation points $t_{n+1}, t_n, \dots, t_{n+2-r}$:

$$\mathcal{P}_1(\tau) \equiv \sum_{j=-1}^{r-2} e^{j\mathbf{A}\Delta t} \mathcal{F}(\mathbf{U}_{n-j}) p_j(\tau), \quad \mathcal{P}_2(\tau) \equiv \sum_{j=-1}^{r-2} \mathcal{G}(t_n - j\Delta t) p_j(\tau), \quad 0 \leq \tau \leq \Delta t,$$

where

$$p_j(\tau) = \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t}. \quad (1.63)$$

In terms of $\mathcal{P}_1(\tau)$ and $\mathcal{P}_2(\tau)$ (1.62) takes the form,

$$\mathbf{U}_{n+1} = e^{\mathbf{A}\Delta t} \mathbf{U}_n + e^{\mathbf{A}\Delta t} \left(\int_0^{\Delta t} \mathcal{P}_1(\tau) d\tau + \int_0^{\Delta t} e^{-\mathbf{A}\tau} \mathcal{P}_2(\tau) d\tau \right). \quad (1.64)$$

So the new r th order implicit schemes are

$$\begin{aligned} \mathbf{U}_{n+1} = & e^{\mathbf{A}\Delta t} \mathbf{U}_n + \Delta t \left(\alpha_1 \mathcal{F}(\mathbf{U}_{n+1}) + \sum_{j=0}^{r-2} \alpha_{-j} e^{(j+1)\mathbf{A}\Delta t} \mathcal{F}(\mathbf{U}_{n-j}) \right. \\ & \left. + e^{\mathbf{A}\Delta t} \sum_{j=-1}^{r-2} \beta_{-j} \mathcal{G}(t_n - j\Delta t) \right), \end{aligned} \quad (1.65)$$

where $\alpha_1, \alpha_0, \alpha_{-1}, \dots, \alpha_{-r+2}$ and $\beta_1, \beta_0, \beta_{-1}, \dots, \beta_{-r+2}$ are coefficients calculated from the integrals of the polynomials $\mathcal{P}_1(\tau)$ and $\mathcal{P}_2(\tau)$, respectively,

$$\begin{aligned} \alpha_{-j} &= \frac{1}{\Delta t} \int_0^{\Delta t} \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t} d\tau, \\ \beta_{-j} &= \frac{1}{\Delta t} \int_0^{\Delta t} e^{-\mathbf{A}\tau} \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t} d\tau, \quad -1 \leq j \leq r-2. \end{aligned} \quad (1.66)$$

In Table (1.1), the values of the coefficients α_{-j} for schemes of order up to four are listed.

Table 1.1: Values of α_{-j} in (1.66) up to order three.

r	α_1	α_0	α_{-1}	α_{-2}
1	1	0	0	0
2	$\frac{1}{2}$	$\frac{1}{2}$	0	0
3	$\frac{5}{12}$	$\frac{2}{3}$	$-\frac{1}{12}$	0
4	$\frac{9}{24}$	$\frac{19}{24}$	$-\frac{5}{24}$	$\frac{1}{24}$

Define the matrices

$$\begin{aligned}\xi_0 &= \mathbf{A}^{-1} \left(\frac{1}{\Delta t} \mathbf{I} - \frac{1}{\Delta t} e^{-\mathbf{A}\Delta t} \right) \\ \xi_k &= \mathbf{A}^{-1} \left(\frac{k}{\Delta t^{k+1}} \xi_{k-1} - \frac{1}{\Delta t} e^{-\mathbf{A}\Delta t} \right) \quad k \geq 1.\end{aligned}\tag{1.67}$$

Then the coefficients β_{-j} for schemes of order up to four are listed in Table (1.2).

Table 1.2: Values of β_{-j} in (1.66) up to order three where ξ_k is defined in (1.67)

r	β_1	β_0	β_{-1}	β_{-2}
1	ξ_0	0	0	0
2	ξ_1	$-\xi_1 + \xi_0$	0	0
3	$\frac{1}{2}\xi_2 + \frac{1}{2}\xi_1$	$-\xi_2 + \xi_0$	$\frac{1}{2}\xi_2 - \frac{1}{2}\xi_1$	0
4	$\frac{1}{6}\xi_3 + \frac{1}{2}\xi_2 + \frac{1}{3}\xi_1$	$-\frac{1}{2}\xi_3 - \xi_2 + \frac{1}{2}\xi_1 + \xi_0$	$\frac{1}{2}\xi_3 + \frac{1}{2}\xi_2 - \xi_1$	$-\frac{1}{6}\xi_3 + \frac{1}{6}\xi_1$

Remark 1: Even though the integration factor method are derived in the context of inhomogeneous Neumann boundary conditions, it can be similarly extended to inhomogeneous Dirichlet boundary conditions.

1.3.2 TWO-DIMENSIONS

Now we consider a two-dimensional reaction-diffusion equation with inhomogeneous Neumann boundary conditions:

$$\begin{cases} \frac{\partial \mathbf{u}}{\partial t} = D \left(\frac{\partial^2 \mathbf{u}}{\partial x^2} + \frac{\partial^2 \mathbf{u}}{\partial y^2} \right) + \mathbf{F}(\mathbf{u}), & (x, y) \in \Omega, \quad t \in [0, T] \\ \frac{\partial \mathbf{u}}{\partial x}(t, x, y) = g_1(t, x, y) & (x, y) \in \partial\Omega, \quad t \in [0, T] \\ \frac{\partial \mathbf{u}}{\partial y}(t, x, y) = g_2(t, x, y) & (x, y) \in \partial\Omega, \quad t \in [0, T] \end{cases}, \tag{1.68}$$

where $\Omega = [a, b] \times [c, d]$. We first discretize the spatial domain by the mesh: $(x_i, y_j) = (a + i \times h_x, c + j \times h_y)$ where $h_x = (b - a)/N_x$, $h_y = (d - c)/N_y$, and $0 \leq i \leq N_x$ and $0 \leq j \leq N_y$. Using the fourth order central difference discretization on the diffusion, we obtain a system of nonlinear ODEs

$$\begin{aligned} \frac{du_{i,j}}{dt} = D & \left(\frac{-u_{i+2,j} + 16u_{i+1,j} - 30u_{i,j} + 16u_{i-1,j} - u_{i-2,j}}{12h_x^2} \right. \\ & \left. + \frac{-u_{i,j+2} + 16u_{i,j+1} - 30u_{i,j} + 16u_{i,j-1} - u_{i,j-2}}{12h_y^2} \right) + \mathbf{F}(u_{i,j}) + \mathbf{G}_1 + \mathbf{G}_2. \end{aligned} \quad (1.69)$$

Next we define matrices \mathbf{U} , \mathcal{G}_1 , \mathcal{G}_2 , \mathbf{A} , and \mathbf{B} by

$$\mathbf{U} = \begin{pmatrix} u_{0,0} & u_{0,1} & \cdots & u_{0,N_y} & u_{0,N_y} \\ u_{1,0} & u_{1,1} & \cdots & u_{1,N_y} & u_{1,N_y} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ u_{N_x,0} & u_{N_x,1} & \cdots & u_{N_x,N_y} & u_{N_x,N_y} \end{pmatrix}_{(N_x+1) \times (N_y+1)}, \quad (1.70)$$

$$\mathcal{G}_1 = \frac{D}{h} \times \begin{pmatrix} -\frac{17g_1(t,x_0,y_0)}{6} & -\frac{17g_1(t,x_0,y_1)}{6} & \cdots & -\frac{17g_1(t,x_0,y_N)}{6} \\ \frac{11g_1(t,x_0,y_0)}{48} & \frac{11g_1(t,x_0,y_1)}{48} & \cdots & \frac{11g_1(t,x_0,y_N)}{48} \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \\ -\frac{11g_1(t,x_N,y_0)}{48} & -\frac{11g_1(t,x_N,y_1)}{48} & \cdots & -\frac{11g_1(t,x_N,y_N)}{48} \\ \frac{17g_1(t,x_N,y_0)}{6} & \frac{17g_1(t,x_N,y_1)}{6} & \cdots & \frac{17g_1(t,x_N,y_N)}{6} \end{pmatrix}_{(N_x+1) \times (N_y+1)}, \quad (1.71)$$

$$\mathcal{G}_2 = \frac{D}{h} \times \begin{pmatrix} -\frac{17g_1(t,x_0,y_0)}{6} & \frac{11g_1(t,x_0,y_0)}{48} & 0 & \cdots \\ -\frac{17g_1(t,x_1,y_0)}{6} & \frac{11g_1(t,x_1,y_0)}{48} & 0 & \cdots \\ \vdots & \vdots & \vdots & \ddots \\ -\frac{17g_1(t,x_N,y_0)}{6} & \frac{11g_1(t,x_N,y_0)}{48} & 0 & \cdots \end{pmatrix} \quad (1.72)$$

$$\left(\begin{array}{cccc} \dots & 0 & -\frac{11g_1(t,x_0,y_N)}{48} & \frac{17g_1(t,x_0,y_N)}{6} \\ \dots & 0 & -\frac{11g_1(t,x_1,y_N)}{48} & \frac{17g_1(t,x_1,y_N)}{6} \\ \ddots & \vdots & \vdots & \vdots \\ \dots & 0 & -\frac{11g_1(t,x_N,y_N)}{48} & \frac{17g_1(t,x_N,y_0)}{6} \end{array} \right)_{(N_x+1) \times (N_y+1)}, \quad (1.73)$$

$$\mathbf{A} = \frac{D}{12h_x^2} \times \left(\begin{array}{ccccc} -\frac{215}{6} & 32 & 12 & -\frac{32}{3} & \frac{5}{2} \\ \frac{803}{48} & -31 & \frac{57}{4} & \frac{1}{3} & -\frac{5}{16} \\ -1 & 16 & -30 & 16 & -1 \\ & -1 & 16 & -30 & 16 & -1 \\ & & \ddots & \ddots & \ddots & \ddots & \ddots \\ & & & -1 & 16 & -30 & 16 & -1 \\ & & & -\frac{5}{16} & \frac{1}{3} & \frac{57}{4} & -31 & \frac{803}{48} \\ & & & \frac{5}{2} & -\frac{32}{3} & 12 & 32 & -\frac{215}{6} \end{array} \right)_{(N_x+1) \times (N_x+1)}, \quad (1.74)$$

and

$$\mathbf{B} = \frac{D}{12h_y^2} \times \left(\begin{array}{ccccccc} -\frac{215}{6} & \frac{803}{48} & -1 & & & & \\ 32 & -31 & 16 & -1 & & & \\ 12 & \frac{57}{4} & -30 & 16 & \ddots & & \\ -\frac{32}{3} & \frac{1}{3} & 16 & -30 & \ddots & -1 & -\frac{5}{16} & \frac{5}{2} \\ \frac{5}{2} & -\frac{5}{16} & -1 & 16 & \ddots & 16 & \frac{1}{3} & -\frac{32}{3} \\ & & & -1 & \ddots & -30 & \frac{57}{4} & 12 \\ & & & & \ddots & 16 & -31 & 32 \\ & & & & & -1 & \frac{803}{48} & -\frac{215}{6} \end{array} \right)_{(N_y+1) \times (N_y+1)} \quad (1.75)$$

In terms of these matrices, the semi-discretized form (1.70) becomes

$$\frac{d\mathbf{U}}{dt} = \mathbf{A}\mathbf{U} + \mathbf{U}\mathbf{B} + \mathcal{F}(\mathbf{U}) + \mathcal{G}_1 + \mathcal{G}_2. \quad (1.76)$$

Since \mathbf{A} and \mathbf{B} can be diagonalized,

$$\mathbf{A} = \mathbf{P}_\mathbf{A} \mathbf{D}_\mathbf{A} \mathbf{P}_\mathbf{A}^{-1} \quad \mathbf{B} = \mathbf{P}_\mathbf{B} \mathbf{D}_\mathbf{B} \mathbf{P}_\mathbf{B}^{-1}.$$

Multiplying (1.76) on the left by $\mathbf{P}_\mathbf{A}^{-1}$ and on the right by $\mathbf{P}_\mathbf{B}$ yields

$$\begin{aligned} \frac{d(\mathbf{P}_\mathbf{A}^{-1} \mathbf{U} \mathbf{P}_\mathbf{B})}{dt} &= \mathbf{D}_\mathbf{A} \mathbf{P}_\mathbf{A}^{-1} \mathbf{U} \mathbf{P}_\mathbf{B} + \mathbf{P}_\mathbf{A}^{-1} \mathbf{U} \mathbf{P}_\mathbf{B} \mathbf{D}_\mathbf{B} \\ &\quad + \mathbf{P}_\mathbf{A}^{-1} \mathcal{F}(\mathbf{U}) \mathbf{P}_\mathbf{B} + \mathbf{P}_\mathbf{A}^{-1} \mathcal{G}_1 \mathbf{P}_\mathbf{B} + \mathbf{P}_\mathbf{A}^{-1} \mathcal{G}_2 \mathbf{P}_\mathbf{B}. \end{aligned} \quad (1.77)$$

Let

$$\mathbf{V} = \mathbf{P}_\mathbf{A}^{-1} \mathbf{U} \mathbf{P}_\mathbf{B}, \quad \tilde{\mathcal{F}} = \mathbf{P}_\mathbf{A}^{-1} \mathcal{F} \mathbf{P}_\mathbf{B}, \quad \tilde{\mathcal{G}}_1 = \mathbf{P}_\mathbf{A}^{-1} \mathcal{G}_1 \mathbf{P}_\mathbf{B}, \quad \tilde{\mathcal{G}}_2 = \mathbf{P}_\mathbf{A}^{-1} \mathcal{G}_2 \mathbf{P}_\mathbf{B}.$$

Then (1.77) becomes

$$\frac{d\mathbf{V}}{dt} = \mathbf{D}_\mathbf{A} \mathbf{V} + \mathbf{V} \mathbf{D}_\mathbf{B} + \tilde{\mathcal{F}}(\mathbf{P}_\mathbf{A} \mathbf{V} \mathbf{P}_\mathbf{B}^{-1}) + \tilde{\mathcal{G}}_1 + \tilde{\mathcal{G}}_2. \quad (1.78)$$

To apply the integration factor technique to the compact discretization form (1.78), we multiply (1.78) by the exponential matrix $e^{-\mathbf{D}_\mathbf{A} t}$ on the left, and $e^{-\mathbf{D}_\mathbf{B} t}$ on the right and take integration over one time step from t_n to $t_{n+1} \equiv t_n + \Delta t$, where Δt is the time step. It leads to

$$\begin{aligned} \mathbf{V}_{n+1} &= e^{\mathbf{D}_\mathbf{A} \Delta t} \mathbf{V}_n e^{\mathbf{D}_\mathbf{B} \Delta t} + e^{\mathbf{D}_\mathbf{A} \Delta t} \left(\int_0^{\Delta t} e^{-\mathbf{D}_\mathbf{A} \tau} \tilde{\mathcal{F}}(\mathbf{P}_\mathbf{A} \mathbf{V}(t_n + \tau) \mathbf{P}_\mathbf{B}^{-1}) e^{-\mathbf{D}_\mathbf{B} \tau} d\tau \right. \\ &\quad \left. + \int_0^{\Delta t} e^{-\mathbf{D}_\mathbf{A} \tau} \tilde{\mathcal{G}}_1(t_n + \tau) e^{-\mathbf{D}_\mathbf{B} \tau} d\tau + \int_0^{\Delta t} e^{-\mathbf{D}_\mathbf{A} \tau} \tilde{\mathcal{G}}_2(t_n + \tau) e^{-\mathbf{D}_\mathbf{B} \tau} d\tau \right) e^{\mathbf{D}_\mathbf{B} \Delta t}. \end{aligned} \quad (1.79)$$

Similar to one-dimensional case, to construct a scheme of r th order truncation error, we approximate the integrands in (1.79) using a $(r-1)$ th order Lagrange polynomial at a set of interpolation points $t_{n+1}, t_n, \dots, t_{n+2-r}$:

$$\begin{aligned} \mathcal{P}_1(\tau) &\equiv \sum_{j=-1}^{r-2} e^{j \mathbf{D}_\mathbf{A} \Delta t} \tilde{\mathcal{F}}(\mathbf{P}_\mathbf{A} \mathbf{V}_{n-j} \mathbf{P}_\mathbf{B}^{-1}) e^{j \mathbf{D}_\mathbf{B} \Delta t} p_j(\tau), \\ \mathcal{P}_2(\tau) &\equiv \sum_{j=-1}^{r-2} \tilde{\mathcal{G}}_1(t_n - j \Delta t) p_j(\tau), \quad \mathcal{P}_3(\tau) \equiv \sum_{j=-1}^{r-2} \tilde{\mathcal{G}}_2(t_n - j \Delta t) p_j(\tau), \quad 0 \leq \tau \leq \Delta t, \end{aligned} \quad (1.80)$$

where

$$p_j(\tau) = \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t}. \quad (1.81)$$

In terms of $\mathcal{P}_i(\tau)$, $i = 1, 2, 3$, (1.79) takes the form,

$$\begin{aligned} \mathbf{V}_{n+1} = & e^{\mathbf{D}_A \Delta t} \mathbf{V}_n e^{\mathbf{D}_B \Delta t} + e^{\mathbf{D}_A \Delta t} \left(\int_0^{\Delta t} \mathcal{P}_1(\tau) d\tau \right. \\ & \left. + \int_0^{\Delta t} e^{-\mathbf{D}_A \tau} \mathcal{P}_2(\tau) e^{-\mathbf{D}_B \tau} d\tau + \int_0^{\Delta t} e^{-\mathbf{D}_A \tau} \mathcal{P}_3(\tau) e^{-\mathbf{D}_B \tau} d\tau \right) e^{\mathbf{D}_B \Delta t}. \end{aligned} \quad (1.82)$$

Let $\mathbf{D}_A = \text{diag}(d_0^a, d_1^a, \dots, d_{N_x}^a)$ and $\mathbf{D}_B = \text{diag}(d_0^b, d_1^b, \dots, d_{N_y}^b)$. Note that multiplication of diagonal matrices on the left and right becomes component-wise matrix multiplication of the form

$$(\mathbf{D}_A \mathcal{G} \mathbf{D}_B)_{i,j} = d_i^a (\mathcal{G})_{i,j} d_j^b. \quad (1.83)$$

So the second integration in (1.82) can be done component-wise. Now the new r th order implicit schemes are

$$\begin{aligned} \mathbf{V}_{n+1} = & e^{\mathbf{D}_A \Delta t} \mathbf{V}_n e^{\mathbf{D}_B \Delta t} + \Delta t \left(\alpha_1 \tilde{\mathcal{F}}(\mathbf{P}_A \mathbf{V}_{n+1} \mathbf{P}_B^{-1}) \right. \\ & \left. + \sum_{j=0}^{r-2} \alpha_{-j} e^{(j+1)\mathbf{D}_A \Delta t} \tilde{\mathcal{F}}(\mathbf{P}_A \mathbf{V}_{n-j} \mathbf{P}_B^{-1}) e^{(j+1)\mathbf{D}_B \Delta t} \right) \\ & + \Delta t e^{\mathbf{D}_A \Delta t} \left(\sum_{j=-1}^{r-2} \beta_{-j} \circ \tilde{\mathcal{G}}_1(t_n - j\Delta t) + \sum_{j=-1}^{r-2} \beta_{-j} \circ \tilde{\mathcal{G}}_2(t_n - j\Delta t) \right) e^{\mathbf{D}_B \Delta t}, \end{aligned} \quad (1.84)$$

where \circ denotes component-wise matrix multiplication and $\alpha_1, \alpha_0, \alpha_{-1}, \dots, \alpha_{-r+2}$ and $\beta_1, \beta_0, \beta_{-1}, \dots, \beta_{-r+2}$ are coefficients calculated from the integrals of the polynomials,

$$\begin{aligned} \alpha_{-j} = & \frac{1}{\Delta t} \int_0^{\Delta t} \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t} d\tau \\ \beta_{-j} = & \frac{1}{\Delta t} \int_0^{\Delta t} e^{-(\mathbf{D}_A + \mathbf{D}_B)\tau} \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t} d\tau, \quad -1 \leq j \leq r-2. \end{aligned} \quad (1.85)$$

In Table (1.1), the values of the coefficients α_{-j} for schemes of order up to three are listed. Define the matrices

$$(\xi_0)_{i,j} = \frac{1}{d_i^a + d_j^b} \left(\frac{1}{\Delta t} - \frac{1}{\Delta t} e^{-(d_i^a + d_j^b)\Delta t} \right)$$

$$(\xi_k)_{i,j} = \frac{1}{d_i^a + d_j^b} \left(\frac{k}{\Delta t^{k+1}} (\xi_{k-1})_{i,j} - \frac{1}{\Delta t} e^{-(d_i^a + d_j^b)\Delta t} \right) \quad k \geq 1. \quad (1.86)$$

Then the coefficients β_{-j} for schemes of order up to three are listed in Table (1.2).

From here the solution of \mathbf{U} can be recovered by $\mathbf{U} = \mathbf{P}_\mathbf{A} \mathbf{V} \mathbf{P}_\mathbf{B}^{-1}$.

Remark 2: For the cases when A or B can not be diagonalized, the terms from inhomogeneous boundary terms can be incorporated into the nonlinear term \mathcal{F} . For instance, the equation (1.76) can be written as

$$\frac{d\mathbf{U}}{dt} = \mathbf{A}\mathbf{U} + \mathbf{U}\mathbf{B} + \bar{\mathcal{F}}(\mathbf{U}). \quad (1.87)$$

where $\bar{\mathcal{F}}(\mathbf{U}) = \mathcal{F}(\mathbf{U}) + \mathcal{G}_1 + \mathcal{G}_2$. We can follow the same ideas for compact implicit integration factor (cIIF) method as discussed in [8]. For instance, the second order cIIF2 method is given by

$$\mathbf{U}_{n+1} = e^{\mathbf{A}\Delta t} \mathbf{U}_n e^{\mathbf{B}\Delta t} + \frac{\Delta t}{2} \left(\bar{\mathcal{F}}(\mathbf{U}_n) + \bar{\mathcal{F}}(\mathbf{U}_{n+1}) \right).$$

1.3.3 THREE-DIMENSIONS

Now we consider a three-dimensional reaction-diffusion equation with Neumann boundary conditions:

$$\left\{ \begin{array}{l} \frac{\partial \mathbf{u}}{\partial t} = D\Delta u + \mathbf{F}(\mathbf{u}), \quad (x, y, z) \in \Omega, \quad t \in [0, T] \\ \frac{\partial \mathbf{u}}{\partial x}(t, x, y, z) = g_1(t, x, y, z) \quad (x, y, z) \in \partial\Omega, \quad t \in [0, T] \\ \frac{\partial \mathbf{u}}{\partial y}(t, x, y, z) = g_2(t, x, y, z) \quad (x, y, z) \in \partial\Omega, \quad t \in [0, T] \\ \frac{\partial \mathbf{u}}{\partial z}(t, x, y, z) = g_3(t, x, y, z) \quad (x, y, z) \in \partial\Omega, \quad t \in [0, T] \end{array} \right. \quad (1.88)$$

where $\Omega = [a_l, a_u] \times [b_l, b_u] \times [c_l, c_u]$. Let N_x, N_y, N_z denote the number of spatial grid points in x, y, z -direction, respectively, h_x, h_y, h_z be the grid size, and $u_{i,j,k}$ represent the approximate solution at the grid point (x_i, y_j, z_k) , $0 \leq i \leq N_x$, $0 \leq j \leq N_y$, and $0 \leq k \leq N_z$. A fourth order central difference discretization on the Lapacian operator yields

$$\frac{du_{i,j,k}}{dt} = D \left(\frac{-u_{i+2,j,k} + 16u_{i+1,j,k} - 30u_{i,j,k} + 16u_{i-1,j,k} - u_{i-2,j,k}}{12h_x^2} \right)$$

$$\begin{aligned}
& + \frac{-u_{i,j+2,k} + 16u_{i,j+1,k} - 30u_{i,j,k} + 16u_{i,j-1,k} - u_{i,j-2,k}}{12h_y^2} \\
& + \frac{-u_{i,j,k+2} + 16u_{i,j,k+1} - 30u_{i,j,k} + 16u_{i,j,k-1} - u_{i,j,k-2}}{12h_z^2} \Big) \\
& + \mathbf{F}(u_{i,j,k}) + \mathbf{G}_{i,j,k}
\end{aligned} \tag{1.89}$$

Define $A_x = \frac{D}{h_x^2} A_{(N_x+1) \times (N_x+1)}$, $A_y = \frac{D}{h_y^2} A_{(N_y+1) \times (N_y+1)}$, and $A_z = \frac{D}{h_z^2} A_{(N_z+1) \times (N_z+1)}$, where

$$A_{P \times P} = \begin{pmatrix} -\frac{215}{6} & 32 & 12 & -\frac{32}{3} & \frac{5}{2} & & & \\ \frac{803}{48} & -31 & \frac{57}{4} & \frac{1}{3} & -\frac{5}{16} & & & \\ -1 & 16 & -30 & 16 & -1 & & & \\ & -1 & 16 & -30 & 16 & -1 & & \\ & & \ddots & \ddots & \ddots & \ddots & \ddots & \\ & & & -1 & 16 & -30 & 16 & -1 \\ & & & -\frac{5}{16} & \frac{1}{3} & \frac{57}{4} & -31 & \frac{803}{48} \\ & & & \frac{5}{2} & -\frac{32}{3} & 12 & 32 & -\frac{215}{6} \end{pmatrix}_{P \times P}.$$

Then (1.89) has the following compact representation

$$\mathbf{U}_t = \left(\sum_{l=0}^{N_x} (A_x)_{i,l} u_{l,j,k} + \sum_{l=0}^{N_y} (A_y)_{j,l} u_{i,l,k} + \sum_{l=0}^{N_z} (A_z)_{k,l} u_{i,j,l} \right) + \mathcal{F}(\mathbf{U}) + \mathcal{G} \tag{1.90}$$

where $\mathbf{U} = (u_{i,j,k})$, $\mathcal{F}(\mathbf{U}) = (\mathcal{F}(u_{i,j,k}))$, and $\mathcal{G} = (\mathcal{G}_{i,j,k})$. \mathcal{G} is defined as

$$\mathcal{G}_{0,j,k} = \frac{D}{h} \times \begin{pmatrix} -\frac{17g_1(t, x_0, y_0, z_0)}{6} & \dots & -\frac{17g_1(t, x_0, y_0, z_{N_z})}{6} \\ \vdots & \ddots & \vdots \\ -\frac{17g_1(t, x_0, y_{N_y}, z_0)}{6} & \dots & -\frac{17g_1(t, x_0, y_{N_y}, z_{N_z})}{6} \end{pmatrix}_{(N_y+1) \times (N_z+1)},$$

$$\mathcal{G}_{1,j,k} = \frac{D}{h} \times \begin{pmatrix} \frac{11g_1(t, x_0, y_0, z_0)}{48} & \dots & \frac{11g_1(t, x_0, y_0, z_{N_z})}{48} \\ \vdots & \ddots & \vdots \\ \frac{11g_1(t, x_0, y_{N_y}, z_0)}{48} & \dots & \frac{11g_1(t, x_0, y_{N_y}, z_{N_z})}{48} \end{pmatrix}_{(N_y+1) \times (N_z+1)},$$

$$\mathcal{G}_{Nx-1,j,k} = \frac{D}{h} \times \begin{pmatrix} -\frac{11g_1(t,x_N,y_0,z_0)}{48} & \dots & -\frac{11g_1(t,x_N,y_0,z_{N_z})}{48} \\ \vdots & \ddots & \vdots \\ -\frac{11g_1(t,x_N,y_{N_y},z_0)}{48} & \dots & -\frac{11g_1(t,x_N,y_{N_y},z_{N_z})}{48} \end{pmatrix}_{(N_y+1) \times (N_z+1)},$$

$$\mathcal{G}_{Nx,j,k} = \frac{D}{h} \times \begin{pmatrix} \frac{17g_1(t,x_N,y_0,z_0)}{6} & \dots & \frac{17g_1(t,x_N,y_0,z_{N_z})}{6} \\ \vdots & \ddots & \vdots \\ \frac{17g_1(t,x_N,y_{N_y},z_0)}{6} & \dots & \frac{17g_1(t,x_N,y_{N_y},z_{N_z})}{6} \end{pmatrix}_{(N_y+1) \times (N_z+1)},$$

$\mathcal{G}_{i,0,k}$, $\mathcal{G}_{i,1,k}$, $\mathcal{G}_{i,N_y-1,k}$, $\mathcal{G}_{i,N_y,k}$, and $\mathcal{G}_{i,j,0}$, $\mathcal{G}_{i,j,1}$, \mathcal{G}_{i,j,N_z-1} , \mathcal{G}_{i,j,N_z} are similarly defined.

For $i \neq 0, 1, N_x - 1, N_x$, $j \neq 0, 1, N_y - 1, N_y$, and $k \neq 0, 1, N_z - 1, N_z$, $\mathcal{G}_{i,j,k} = 0$.

The three summation terms in (1.90) are similar to the two vector-matrix multiplications in the two-dimensional case in (1.76). In addition to a left multiplication and a right multiplication in (1.76), there is a "middle" multiplication in (1.90).

Since A_γ can be diagonalized,

$$A_\gamma = P_\gamma D_\gamma P_\gamma^{-1} \quad \gamma = x, y, z. \quad (1.91)$$

Define an operator \mathcal{D} by

$$(\mathcal{D}\mathbf{U})_{i,j,k} = \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{d=0}^{N_x} (P_z^{-1})_{k,f} (P_y^{-1})_{j,e} (P_x^{-1})_{i,d} u_{d,e,f}. \quad (1.92)$$

Applying \mathcal{D} to the first term of (1.90) yields

$$\begin{aligned} (\mathcal{D}\mathbf{U}_t)^{\text{1st term}} &= \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{d=0}^{N_x} (P_z^{-1})_{k,f} (P_y^{-1})_{j,e} (P_x^{-1})_{i,d} \sum_{l=0}^{N_x} (P_x D_x P_x^{-1})_{d,l} u_{l,e,f} \\ &= \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{l=0}^{N_x} (P_z^{-1})_{k,f} (P_y^{-1})_{j,e} \sum_{d=0}^{N_x} (P_x^{-1})_{i,d} (P_x D_x P_x^{-1})_{d,l} u_{l,e,f} \\ &= \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{l=0}^{N_x} (P_z^{-1})_{k,f} (P_y^{-1})_{j,e} (D_x P_x^{-1})_{i,l} u_{l,e,f} \\ &= \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{l=0}^{N_x} (P_z^{-1})_{k,f} (P_y^{-1})_{j,e} \sum_{a=0}^{N_x} (D_x)_{i,a} (P_x^{-1})_{a,l} u_{l,e,f} \end{aligned}$$

$$\begin{aligned}
&= \sum_{a=0}^{N_x} (D_x)_{i,a} \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{l=0}^{N_x} (P_z^{-1})_{k,f} (P_y^{-1})_{j,e} (P_x^{-1})_{a,l} u_{l,e,f} \\
&= \sum_{a=0}^{N_x} (D_x)_{i,a} (\mathcal{D}\mathbf{U})_{a,j,k}
\end{aligned} \tag{1.93}$$

Make the following substitutions,

$$\mathbf{V} = \mathcal{D}\mathbf{U}, \quad \tilde{\mathcal{F}} = \mathcal{D}\mathcal{F}, \quad \tilde{\mathcal{G}} = \mathcal{D}\mathcal{G}.$$

Then applying \mathcal{D} to (1.90) yields

$$\mathbf{V}_t = \left(\sum_{l=0}^{N_x} (D_x)_{i,l} v_{l,j,k} + \sum_{l=0}^{N_y} (D_y)_{j,l} v_{i,l,k} + \sum_{l=0}^{N_z} (D_z)_{k,l} v_{i,j,l} \right) + \tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}) + \tilde{\mathcal{G}} \tag{1.94}$$

Define an operator $\mathcal{L}(t)$ by

$$(\mathcal{L}(t)\mathbf{U})_{i,j,k} = \sum_{n=0}^{N_z} \sum_{m=0}^{N_y} \sum_{l=0}^{N_x} (e^{-D_z t})_{k,n} (e^{-D_y t})_{j,m} (e^{-D_x t})_{i,l} u_{l,m,n}. \tag{1.95}$$

Taking derivatives of (1.95) yields

$$\frac{d\mathcal{L}(t)\mathbf{U}}{dt} = \mathcal{L}(t) \left(\mathbf{U}_t - \left(\sum_{l=0}^{N_x} (D_x)_{i,l} u_{l,j,k} + \sum_{l=0}^{N_y} (D_y)_{j,l} u_{i,l,k} + \sum_{l=0}^{N_z} (D_z)_{k,l} u_{i,j,l} \right) \right). \tag{1.96}$$

Letting $\mathcal{L}(t)$ act on both sides of (1.94) and using (1.96), we obtain

$$\frac{d\mathcal{L}(t)\mathbf{V}}{dt} = \mathcal{L}(t)\tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}) + \mathcal{L}(t)\tilde{\mathcal{G}}. \tag{1.97}$$

Integrating (1.97) over one time step from t_n to t_{n+1} and using a transformation $s = t_n + \tau$ for the integration, we obtain

$$\begin{aligned}
\mathcal{L}(t_{n+1})\mathbf{V}_{n+1} &= \mathcal{L}(t_n)\mathbf{V}_n + \mathcal{L}(t_n) \int_0^{\Delta t} \mathcal{L}(\tau) \tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}(t_n + \tau)) d\tau \\
&\quad + \mathcal{L}(t_n) \int_0^{\Delta t} \mathcal{L}(\tau) \tilde{\mathcal{G}}(t_n + \tau) d\tau.
\end{aligned} \tag{1.98}$$

Applying $\mathcal{L}(-t_{n+1})$ on both sides of (1.98) yields

$$\begin{aligned}
\mathbf{V}_{n+1} &= \mathcal{L}(-\Delta t)\mathbf{V}_n + \mathcal{L}(-\Delta t) \int_0^{\Delta t} \mathcal{L}(\tau) \tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}(t_n + \tau)) d\tau \\
&\quad + \mathcal{L}(-\Delta t) \int_0^{\Delta t} \mathcal{L}(\tau) \tilde{\mathcal{G}}(t_n + \tau) d\tau.
\end{aligned} \tag{1.99}$$

To derive (1.99), we have used two identities:

$$\mathcal{L}(0)\mathbf{V} = \mathbf{V} \quad \text{and} \quad \mathcal{L}(-rt)\mathcal{L}(st)\mathbf{V} = \mathcal{L}((s-r)t)\mathbf{V} \quad (1.100)$$

for any two scalars r and s . Both of these can be easily proved based on the definition of \mathcal{L} .

Similar to one and two dimensional cases, to construct a scheme of r th order truncation error, we approximate the integrands in (1.99) using a $(r-1)$ th order Lagrange polynomial at a set of interpolation points $t_{n+1}, t_n, \dots, t_{n+2-r}$:

$$\begin{aligned} \mathcal{P}_1(\tau) &\equiv \sum_{j=-1}^{r-2} \mathcal{L}(-j\Delta t) \tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}_{n-j}) p_j(\tau), \\ \mathcal{P}_2(\tau) &\equiv \sum_{j=-1}^{r-2} \tilde{\mathcal{G}}(t_n - j\Delta t) p_j(\tau), \quad 0 \leq \tau \leq \Delta t, \end{aligned} \quad (1.101)$$

where

$$p_j(\tau) = \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t}. \quad (1.102)$$

In terms of $\mathcal{P}_i(\tau)$, $i = 1, 2$, (1.99) takes the form,

$$\mathbf{V}_{n+1} = \mathcal{L}(-\Delta t)\mathbf{V}_n + \mathcal{L}(-\Delta t) \left(\int_0^{\Delta t} \mathcal{P}_1(\tau) d\tau + \int_0^{\Delta t} \mathcal{L}(\tau) \mathcal{P}_2(\tau) d\tau \right) \quad (1.103)$$

So the new r th order implicit schemes are

$$\begin{aligned} \mathbf{V}_{n+1} &= \mathcal{L}(-\Delta t)\mathbf{V}_n + \Delta t \left(\alpha_1 \tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}_{n+1}) + \sum_{j=0}^{r-2} \alpha_{-j} \mathcal{L}(-(j+1)\Delta t) \tilde{\mathcal{F}}(\mathcal{D}^{-1}\mathbf{V}_{n-j}) \right. \\ &\quad \left. + \mathcal{L}(-\Delta t) \sum_{j=-1}^{r-2} \beta_{-j} \circ \tilde{\mathcal{G}}(t_n - j\Delta t) \right), \end{aligned} \quad (1.104)$$

where \circ denotes component-wise multiplication of the three-dimensional matrices, and $\alpha_1, \alpha_0, \alpha_{-1}, \dots, \alpha_{-r+2}$ and $\beta_1, \beta_0, \beta_{-1}, \dots, \beta_{-r+2}$ are coefficients calculated from the integrals of the polynomials,

$$\alpha_{-j} = \frac{1}{\Delta t} \int_0^{\Delta t} \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t} d\tau$$

$$\beta_{-j} = \frac{1}{\Delta t} \int_0^{\Delta t} \mathcal{L}(\tau) \prod_{k=-1, k \neq j}^{r-2} \frac{\tau + k\Delta t}{(k-j)\Delta t} d\tau, \quad -1 \leq j \leq r-2. \quad (1.105)$$

In Table (1.1), the values of the coefficients α_{-j} for schemes of order up to three are listed. Define the matrices

$$\begin{aligned} (\xi_0)_{i,j,k} &= \frac{1}{d_i^x + d_j^y + d_k^z} \left(\frac{1}{\Delta t} - \frac{1}{\Delta t} e^{-(d_i^x + d_j^y + d_k^z)\Delta t} \right) \\ (\xi_\gamma)_{i,j,k} &= \frac{1}{d_i^x + d_j^y + d_k^z} \left(\frac{\gamma}{\Delta t^{\gamma+1}} (\xi_{\gamma-1})_{i,j,k} - \frac{1}{\Delta t} e^{-(d_i^x + d_j^y + d_k^z)\Delta t} \right) \quad \gamma \geq 1. \end{aligned} \quad (1.106)$$

Then the coefficients β_{-j} for schemes of order up to three are listed in Table (1.2).

From here \mathbf{U} can be recovered by $\mathbf{U} = \mathcal{D}^{-1}\mathbf{V}$, where

$$(\mathcal{D}^{-1}\mathbf{U})_{i,j,k} = \sum_{f=0}^{N_z} \sum_{e=0}^{N_y} \sum_{d=0}^{N_x} (P_z)_{k,f} (P_y)_{j,e} (P_x)_{i,d} u_{d,e,f}. \quad (1.107)$$

Remark 3: The scheme (1.104) has a form similar to the one-and two-dimensional case. The evaluation of the nonlinear term \mathcal{F} at t_{n+1} is still local and decoupled from the global diffusion term such that a nonlinear system of the size \mathcal{F} needs to be solved at each spatial grid point. Such approach can also be similarly extended to systems with any high spatial dimensions.

1.4 NUMERICAL EXAMPLES

To study the efficacy and accuracy of the fourth order compact implicit integration factor (cIIF) method, we will implement it on the systems in two- and three-dimensions. We test it on examples with either homogeneous or inhomogeneous boundary conditions for both linear and nonlinear systems. In the calculation, the exponential of the square matrix is computed using "expm" of MATLAB which uses a scaling and squaring algorithm with a Pade approximation.

Because the matrix exponentials depend only on the spatial grid size, the time step, and diffusion coefficient, during the entire temporal updating, they only need to be calculated once initially for a fixed numerical resolution. The local nonlinear systems resulting from cIIF are solved iteratively using Newton's method.

In all examples, the cIIF scheme is implemented with fourth order both in time and space. It is implemented in MATLAB up to $T = 1$ at which the L^∞ difference between the numerical solution and the exact solution is measured. For the cases when the exact solution is not given, we take the numerical solution with relatively fine mesh as the "exact" solution. We set $h_x = h_y$ for the two-dimensional examples and $h_x = h_y = h_z$ for the three-dimensional examples. The inhomogeneous boundary condition algorithm has a higher requirement on the space to time step ratio, $\frac{h}{\Delta t}$, for stability than the homogeneous boundary condition algorithm. So we use a smaller time step for the inhomogeneous examples. The scheme is executed on a PC laptop with Intel Core 2 Solo processor with 4GB RAM. The error, spatial order, and code execution time results are in Tables (1.3) and (1.4). The fourth order accuracy can be observed for all the examples except for example 8, and we believe that the order might be compromised since the selected time step is not sufficiently small, while the simulation takes too long for such a three-dimensional system.

Example 1: linear problem in two-dimensions with homogeneous Neumann boundary conditions

We consider a linear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.2 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + 0.1u, \quad (x, y) \in \Omega = \{0 < x < 2\pi, \pi/2 < y < 5\pi/2\}; \\ \frac{\partial u}{\partial x}(0, y, t) = \frac{\partial u}{\partial x}(2\pi, y, t) = 0; \\ \frac{\partial u}{\partial y}(x, \pi/2, t) = \frac{\partial u}{\partial y}(x, 5\pi/2, t) = 0; \\ u(x, y, 0) = \cos x + \sin y. \end{array} \right. \quad (1.108)$$

The exact solution of the system is

$$u(x, y, t) = e^{-0.1t}(\cos x + \sin y). \quad (1.109)$$

Example 2: nonlinear problem in two-dimensions with homogeneous Neumann boundary conditions

We consider a nonlinear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.2 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + \sin u, \quad (x, y) \in \Omega = \{0 < x < 2\pi, \pi/2 < y < 5\pi/2\}; \\ \frac{\partial u}{\partial x}(0, y, t) = \frac{\partial u}{\partial x}(2\pi, y, t) = 0; \\ \frac{\partial u}{\partial y}(x, \pi/2, t) = \frac{\partial u}{\partial y}(x, 5\pi/2, t) = 0; \\ u(x, y, 0) = \cos x + \sin y. \end{array} \right. \quad (1.110)$$

Since we do not know the exact solution, we treat the calculated solution for a very fine spatial mesh as the exact solution. The fine mesh is $1280 \times 1280 \times 640$, ($N_x \times N_y \times N_t$). The cIIF scheme took about 12.5 hours to calculate the solution on this fine mesh.

Example 3: linear problem in two-dimensions with homogeneous Dirichlet boundary conditions

We consider a linear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.1 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + 0.1u, \quad (x, y) \in \Omega = \{0 < x < 2\pi, \pi/2 < y < 5\pi/2\}; \\ u(0, y, t) = u(2\pi, y, t) = 0; \\ u(x, \pi/2, t) = u(x, 5\pi/2, t) = 0; \\ u(x, y, 0) = \sin x \cos y. \end{array} \right. \quad (1.111)$$

The exact solution of the system is

$$u(x, y, t) = e^{-0.1t} \sin x \cos y. \quad (1.112)$$

Example 4: nonlinear problem in two-dimensions with homogeneous Dirichlet boundary conditions

We consider a nonlinear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.1 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + \sin u, \quad (x, y) \in \Omega = \{0 < x < 2\pi, \pi/2 < y < 5\pi/2\}; \\ u(0, y, t) = u(2\pi, y, t) = 0; \\ u(x, \pi/2, t) = u(x, 5\pi/2, t) = 0; \\ u(x, y, 0) = \sin x \cos y. \end{array} \right. \quad (1.113)$$

Since we do not know the exact solution, we treat the calculated solution for a very fine spatial mesh as the exact solution. The fine mesh is $1280 \times 1280 \times 640$, ($N_x \times N_y \times N_t$). The cIIF scheme took about 11.6 hours to calculate the solution on this fine mesh.

Example 5: linear problem in two-dimensions with inhomogeneous Dirichlet boundary conditions

We consider a linear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.1 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} \right) + 0.1u, \quad (x, y) \in \Omega = \{\pi/2 < x < 5\pi/2, 0 < y < 2\pi\}; \\ u(\pi/2, y, t) = u(5\pi/2, y, t) = e^{-0.1t} \cos y; \\ u(x, 0, t) = u(x, 2\pi, t) = e^{-0.1t} \sin x; \\ u(x, y, 0) = \sin x \cos y. \end{array} \right. \quad (1.114)$$

The exact solution of the system is

$$u(x, y, t) = e^{-0.1t} \sin x \cos y. \quad (1.115)$$

Example 6: linear problem in three-dimensions with homogeneous Dirichlet boundary conditions

We consider a linear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.1 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + 0.2u, \quad (x, y, z) \in \Omega = \{0 < x < 2\pi, \\ \pi/2 < y < 5\pi/2, \pi/2 < z < 5\pi/2\}; \\ u(0, y, z, t) = u(2\pi, y, z, t) = 0; \\ u(x, \pi/2, z, t) = u(x, 5\pi/2, z, t) = 0; \\ u(x, y, \pi/2, t) = u(x, y, 5\pi/2, t) = 0; \\ u(x, y, z, 0) = \sin x \cos y \cos z. \end{array} \right. \quad (1.116)$$

The exact solution of the system is

$$u(x, y, z, t) = e^{-0.1t} \sin x \cos y \cos z. \quad (1.117)$$

Example 7: linear problem in three-dimensions with homogeneous Neumann boundary conditions

We consider a linear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.2 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + 0.1u, \quad (x, y, z) \in \Omega = \{0 < x < 2\pi, \\ \pi/2 < y < 5\pi/2, \pi/2 < z < 5\pi/2\}; \\ \frac{\partial u}{\partial x}(0, y, z, t) = \frac{\partial u}{\partial x}(2\pi, y, z, t) = 0; \\ \frac{\partial u}{\partial y}(x, \pi/2, z, t) = \frac{\partial u}{\partial y}(x, 5\pi/2, z, t) = 0; \\ \frac{\partial u}{\partial z}(x, y, \pi/2, t) = \frac{\partial u}{\partial z}(x, y, 5\pi/2, t) = 0; \\ u(x, y, z, 0) = \cos x + \sin y + \sin z. \end{array} \right. \quad (1.118)$$

The exact solution of the system is

$$u(x, y, t) = e^{-0.1t}(\cos x + \sin y + \sin z). \quad (1.119)$$

Example 8: linear problem in three-dimensions with inhomogeneous Dirichlet boundary conditions

We consider a linear reaction-diffusion equation

$$\left\{ \begin{array}{l} \frac{\partial u}{\partial t} = 0.1 \left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2} \right) + 0.2u, \quad (x, y, z) \in \Omega = \{\pi/2 < x < 5\pi/2, \\ \quad \quad \quad 0 < y < 2\pi, 0 < z < 2\pi\}; \\ u(\pi/2, y, z, t) = u(5\pi/2, y, z, t) = e^{-0.1t} \cos y \cos z; \\ u(x, 0, z, t) = u(x, 2\pi, z, t) = e^{-0.1t} \sin x \cos z; \\ u(x, y, 0, t) = u(x, y, 2\pi, t) = e^{-0.1t} \sin x \cos y; \\ u(x, y, z, 0) = \sin x \cos y \cos z. \end{array} \right. \quad (1.120)$$

The exact solution of the system is

$$u(x, y, z, t) = e^{-0.1t} \sin x \cos y \cos z. \quad (1.121)$$

1.5 CONCLUSIONS

In high spatial dimensions, the compact representation of integration factor approach was found to be very efficient for solving systems involving high-order spatial derivatives and reactions with drastically different time scales, which in general demand temporal schemes with severe stability constraints. In general, it is difficult to develop cIIF with high order accuracy, especially for inhomogeneous boundary conditions. In this chapter, we have developed a cIIF method for solving a class of stiff

Table 1.3: Error, order, and CPU time results of the two-dimensional examples.

$N_x \times N_y \times N_t$	Error	Order	CPU Time (s)
Example 1			
$20 \times 20 \times 640$	3.28×10^{-4}	-	0.10
$40 \times 40 \times 640$	9.08×10^{-6}	5.18	0.45
$80 \times 80 \times 640$	2.04×10^{-7}	5.48	2.57
$160 \times 160 \times 640$	9.93×10^{-9}	4.36	15.43
Example 2			
$20 \times 20 \times 640$	2.09×10^{-3}	-	0.25
$40 \times 40 \times 640$	9.27×10^{-5}	4.49	0.83
$80 \times 80 \times 640$	3.00×10^{-6}	4.95	5.16
$160 \times 160 \times 640$	1.48×10^{-7}	4.34	29.68
Example 3			
$20 \times 20 \times 640$	2.02×10^{-4}	-	0.09
$40 \times 40 \times 640$	1.21×10^{-5}	4.06	0.35
$80 \times 80 \times 640$	4.72×10^{-7}	4.68	2.49
$160 \times 160 \times 640$	1.61×10^{-8}	4.87	14.99
Example 4			
$20 \times 20 \times 640$	2.13×10^{-3}	-	0.20
$40 \times 40 \times 640$	6.24×10^{-5}	5.09	1.08
$80 \times 80 \times 640$	1.52×10^{-5}	2.04	5.03
$160 \times 160 \times 640$	7.96×10^{-7}	4.26	27.92
Example 5			
$20 \times 20 \times 1280$	2.31×10^{-4}	-	1.52
$40 \times 40 \times 1280$	5.35×10^{-6}	5.43	4.74
$80 \times 80 \times 1280$	2.47×10^{-7}	4.44	23.73

reaction-diffusion systems for inhomogeneous boundary conditions with fourth order accuracy in space [16]. In this approach, the stability condition and computational savings and storage are similar to the original cIIF with second order accuracy.

Although the high order IF method has been presented only in the context of implicit integration factor methods for reaction-diffusion equations, such approach can easily be applied to other integration factor or exponential difference methods. Other type of equations of high-order derivatives, (e.g. Cahn-Hilliard equations of fourth-order derivatives) may also potentially be handled using the approach for better efficiency. To better deal with high spatial dimensions, one may incorporate the sparse grid [18, 19] into the compact representation technique. The flexibility of com-

Table 1.4: Error, order, and CPU time results of the three-dimensional examples.

$N_x \times N_y \times N_z \times N_t$	Error	Order	CPU Time (s)
Example 6			
$20 \times 20 \times 20 \times 640$	4.93×10^{-4}	-	17.33
$40 \times 40 \times 40 \times 640$	1.36×10^{-5}	5.18	96.14
$80 \times 80 \times 80 \times 640$	3.06×10^{-7}	5.48	872.26
$160 \times 160 \times 160 \times 640$	1.49×10^{-8}	4.36	9670.20
Example 7			
$20 \times 20 \times 20 \times 640$	1.99×10^{-4}	-	14.66
$40 \times 40 \times 40 \times 640$	1.20×10^{-5}	4.05	85.02
$80 \times 80 \times 80 \times 640$	4.69×10^{-7}	4.67	824.93
$160 \times 160 \times 160 \times 640$	1.60×10^{-8}	4.87	9349.11
Example 8			
$20 \times 20 \times 20 \times 1280$	2.53×10^{-4}	-	351.10
$40 \times 40 \times 40 \times 1280$	5.53×10^{-6}	5.52	3120.31
$80 \times 80 \times 80 \times 1280$	5.53×10^{-7}	3.32	38662.07

compact representation allows either direct calculation of the exponentials of matrices or using Krylov subspace [20–22] for non-constant diffusion coefficients to compute their exponential matrix-vector multiplications for saving further in storages and cost. In addition, the presented approach based on the finite difference framework for spatial discretization could also be extended to other discretization methods such as finite volume [23–25] or spectral methods [26, 27]. Overall, the compact representation along with integration factor methods provides an efficient approach for solving a wide range of problems arising from biological and physical applications. Given to its effectiveness in implementation and good stability conditions, the method is very desirable to be incorporated with local adaptive mesh refinement [10, 28, 29], which will also be further explored in future work.

CHAPTER 2

STABILITY ANALYSIS OF MATHEMATICAL MODELS FOR NONLINEAR GROWTH KINETICS OF BREAST CANCER STEM CELLS¹

2.1 INTRODUCTION

Many cancer patients, including those with breast cancer, suffer from the resurgence of tumors despite receiving various forms of therapy [31]. Since tumors comprise of heterogeneous cell types, researchers propose the cancer stem cell hypothesis to explain the survival and reformation of tumors. This hypothesis attributes tumor resurgence to a small subset of tumor cells, called cancer stem cells (CSCs), which can survive treatment, self-renew, and differentiate to form the heterogeneous bulk of a tumor [32, 33]. As a result of their tumorigenicity, CSCs are a potential target in conjunction with current therapy for more effective cancer treatment [34, 35]. Mathematical modeling is employed to study the growth kinetics of breast CSCs. Such models aid in understanding factors involved in tumor growth and consequentially provide implications for CSC targeted therapy [36–39].

This chapter is largely motivated by the papers [40] and [37]. In [40], via the contraction fixed point theorem, the authors obtained the exponential stability in mean square of the stochastic neutral cellular neural network. In [37], by proposing a mathematical model with three types of tumor cells, the authors explored the growth

¹30.

kinetics of CSC population both in vitro and in vivo. In this chapter, we generalize the model as in [37] to n -cell types with generic coefficient functions. We prove the existence of a unique solution of this system of functional differential equations and study its stability. We then apply these theorems to the specific model that was used in [37]. We conclude with numerical simulations of the model. Consistent with the theories, our numerical examples show that the time delays can disrupt the stability [30].

The chapter is organized as follows. In Section 2.2, some definitions and theorems are introduced in preliminaries. In Section 2.3, we prove the existence and uniqueness of the solution for a generalized model of non-linear growth kinetics of breast cancer stem cells. In Section 2.4, The stability of solutions is studied. In Section 2.5, some examples are given to demonstrate the results. Numerical examples are presented in Section 2.6. Finally we conclude the paper.

2.2 PRELIMINARIES

Here we consider the generalized system of functional differential equations with time delays for the non-linear growth kinetics of breast cancer stem cells

$$\begin{aligned}
\frac{dx_0(t)}{dt} &= [P_0(x_{n-1}(t-\tau)) - Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t) - d_0x_0(t), \\
\frac{dx_1(t)}{dt} &= [1 - P_0(x_{n-1}(t-\tau)) + Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t) \\
&\quad + [P_1(x_{n-1}(t-\tau)) - Q_1(x_{n-1}(t-\tau))]\nu_1(x_{n-1}(t-\tau))x_1(t) - d_1x_1(t), \\
&\quad \vdots \\
\frac{dx_{n-2}(t)}{dt} &= [1 - P_{n-3}(x_{n-1}(t-\tau)) + Q_{n-3}(x_{n-1}(t-\tau))]\nu_{n-3}(x_{n-1}(t-\tau))x_{n-3}(t) \\
&\quad + [P_{n-2}(x_{n-1}(t-\tau)) - Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}(t) \\
&\quad - d_{n-2}x_{n-2}(t), \\
\frac{dx_{n-1}(t)}{dt} &= [1 - P_{n-2}(x_{n-1}(t-\tau)) + Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}(t)
\end{aligned}$$

$$-d_{n-1}x_{n-1}(t) \quad (1.1)$$

for $n \geq 2$. Here we denote $x_i(t)$ the number of cells at time t for cell types $i, i = 0, 1, \dots, n-1$. P_i the probability that the cell type i is divided into a pair of itself, Q_i the probability that the cell type i is divided into a pair of next cell lineage (cell type $i+1$). Thus $1 - P_i - Q_i$ denotes the probability that an asymmetric cell division takes place from cell type i to cell type $i-1$. Here v_i is the synthesis rate which quantifies the speed for cell type i to divide in unit time, d_i is the degradation rate. Here τ is a positive constant, $P_i > 0$, $Q_i > 0$, $\nu_i > 0$ ($i = 0, 1, 2, \dots, n-2$) are all decreasing functions of x_{n-1} , which represents the negative feedback from the terminally differentiated cell type $n-1$.

Since P_i , Q_i , and ν_i ($i = 0, 1, 2, \dots, n-2$) are decreasing functions of x_{n-1} , there exist some positive constants \bar{P}_i , \bar{Q}_i , and $\bar{\nu}_i$ such that

$$P_i(x_{n-1}) \leq \bar{P}_i, \quad Q_i(x_{n-1}) \leq \bar{Q}_i, \quad \nu_i(x_{n-1}) \leq \bar{\nu}_i \quad \text{for } i = 0, 1, 2, \dots, n-2. \quad (1.2)$$

In fact, (1.1) can be written in the more general form

$$\dot{x}(t) = f(t, x(t), x(t-\tau)) \quad (1.3)$$

with the initial condition

$$x(s) = \phi(s) \in C([t_0 - \tau, t_0]; R^n), \quad t_0 - \tau \leq s \leq t_0, \quad (1.4)$$

where τ is a constant and $x(t) = (x_0(t), x_1(t), \dots, x_{n-1}(t))^T$ is the state vector.

Let $B = [b_{ij}(t)]_{n \times n}$ with

$$|x(t)|_1 = \sum_{i=1}^n |x_i(t)|$$

and

$$\|B(t)\|_3 = \sum_{i,j=1}^n |b_{ij}(t)|.$$

We denote by $C([t_0 - \tau, t_0]; R^n)$ the family of all continuous functions $\varphi : [t_0 - \tau, t_0] \rightarrow R^n$ with

$$\|\phi\|_2 = \sup_{t_0 - \tau \leq \theta \leq t_0} |\phi(\theta)|_1.$$

The following definitions in [41] will be used to describe the stability of steady state solution. Suppose $f(t, 0) = 0$ for all $t \in R$.

Definition 2.1. The solution $x = 0$ of Equation (1.3) is said to be *stable* if for all $t_0 \in R$ and $\epsilon > 0$, there exists a $\delta > 0$ such that if $\|\phi\|_2 < \delta$, then $|x(t)|_1 < \epsilon$ for $t \geq t_0$.

Definition 2.2. The solution $x = 0$ of Equation (1.3) is said to be *asymptotically stable* if it is stable and for all $t_0 \in R$, there exists a $b_0 > 0$ such that if $\|\phi\|_2 < b_0$, then $x(t) \rightarrow 0$ as $t \rightarrow \infty$.

Definition 2.3. The solution $x = 0$ of Equation (1.3) is said to be *uniformly stable* if the number δ in the definition of stable is independent of t_0 , i.e., for all $\epsilon > 0$, there exists a $\delta > 0$ such that if $\|\phi\|_2 < \delta$ for some $t_0 \in R$, then $|x(t)|_1 < \epsilon$ for $t \geq t_0$.

Definition 2.4. The solution $x = 0$ of Equation (1.3) is said to be *uniformly asymptotically stable* if it is uniformly stable and there exists a $b_0 > 0$ such that for every $\eta > 0$, there exists an $s > 0$ such that if $\|\phi\|_2 < b_0$, then $|x(t)|_1 < \eta$ for $t \geq t_0 + s$ for all $t_0 \in R$.

The following theorem in [41] will be used to give sufficient conditions for the existence and uniqueness of the solution for the system (1.3).

Theorem A. Suppose Ω is an open set in $R \times C$, $f : \Omega \rightarrow R^n$ is continuous, and $f(t, \phi)$ is Lipschitzian in ϕ in each compact set in Ω . If $(t, \phi) \in \Omega$, then there is a unique solution of Equation (1.3) through (t, ϕ) .

If $V : R \times C \rightarrow R$ is continuous and $x(t, \phi)$ is the solution of Equation (1.3) through (t, ϕ) , we define

$$\dot{V}(t, \phi) = \overline{\lim}_{h \rightarrow 0^+} \frac{1}{h} [V(t + h, x_{t+h}(t, \phi)) - V(t, \phi)].$$

The function $\dot{V}(t, \phi)$ is the upper right-hand derivative of $V(t, \phi)$ along the solution of $x(t, \phi)$.

The following method of Liapunov functionals in [41] will be used to give sufficient conditions for the stability of the solution $x = 0$ for the system (1.3).

Theorem B. Suppose $f : R \times C \rightarrow R^n$ takes $R \times (\text{bounded sets of } C)$ into bounded sets of R^n , $\mu, \nu, \omega : R^+ \rightarrow R^+$ are continuous nondecreasing functions, $\mu(s)$ and $\nu(s)$ are positive for $s > 0$, and $\mu(0) = \nu(0) = 0$. If there is a continuous function $V : R \times C \rightarrow R$ such that

$$\mu(|x|_1) \leq V(t, x) \leq \nu(\|x\|_2)$$

and

$$\dot{V}(t, x) \leq -\omega(|x|_1).$$

Then the solution $x = 0$ of Equation (1.3) is uniformly stable. If $\mu(s) \rightarrow \infty$ as $s \rightarrow \infty$, the solutions of Equation (1.3) are uniformly bounded. If $\omega(s) > 0$ for $s > 0$, then the solution $x = 0$ is uniformly asymptotically stable.

2.3 EXISTENCE OF SOLUTIONS FOR NON-LINEAR GROWTH KINETICS OF BREAST CANCER STEM CELLS

Theorem 3.1. Suppose Ω is an open set in $R \times C$. If $(t, \phi) \in \Omega$, then there is a unique solution of Equation (1.1) through (t, ϕ) .

Proof: Firstly, we have from (1.1) that

$$\dot{x}(t) = F(t, x(t), x(t - \tau)) - Dx(t) \tag{3.1}$$

with the initial condition

$$x(s) = \phi(s) \in C([t_0 - \tau, t_0]; R^n), \quad t_0 - \tau \leq s \leq t_0, \tag{3.2}$$

where $x(t) = (x_0(t), x_1(t), \dots, x_{n-1}(t))^T$, $D = \text{diag}(d_0, d_1, \dots, d_{n-1})$,

$$\begin{aligned}
F(t, x(t), x(t - \tau)) &= \begin{pmatrix} f_1 \\ f_2 \\ \vdots \\ f_{n-2} \\ f_{n-1} \end{pmatrix} = A(x_{n-1}(t - \tau)) \begin{pmatrix} x_0 \\ x_1 \\ \vdots \\ x_{n-2} \\ x_{n-1} \end{pmatrix} \\
&= \begin{pmatrix} [P_0(x_{n-1}(t - \tau)) - Q_0(x_{n-1}(t - \tau))] \nu_0(x_{n-1}(t - \tau)) x_0(t) \\ [1 - P_0(x_{n-1}(t - \tau)) + Q_0(x_{n-1}(t - \tau))] \nu_0(x_{n-1}(t - \tau)) x_0(t) + \\ [P_1(x_{n-1}(t - \tau)) - Q_1(x_{n-1}(t - \tau))] \nu_1(x_{n-1}(t - \tau)) x_1(t) \\ \vdots \\ [1 - P_{n-3}(x_{n-1}(t - \tau)) + Q_{n-3}(x_{n-1}(t - \tau))] \nu_{n-3}(x_{n-1}(t - \tau)) x_{n-3}(t) + \\ [P_{n-2}(x_{n-1}(t - \tau)) - Q_{n-2}(x_{n-1}(t - \tau))] \nu_{n-2}(x_{n-1}(t - \tau)) x_{n-2}(t) \\ [1 - P_{n-2}(x_{n-1}(t - \tau)) + Q_{n-2}(x_{n-1}(t - \tau))] \nu_{n-2}(x_{n-1}(t - \tau)) x_{n-2}(t) \end{pmatrix}, \\
A(x_{n-1}(t - \tau)) &= \begin{pmatrix} [P_0 - Q_0] \nu_0 & 0 & \dots \\ [1 - P_0 + Q_0] \nu_0 & [P_1 - Q_1] \nu_1 & \dots \\ \vdots & \vdots & \ddots \\ 0 & 0 & \dots \\ 0 & 0 & \dots \\ \dots & 0 & 0 & 0 \\ \dots & 0 & 0 & 0 \\ \ddots & \vdots & \vdots & \vdots \\ \dots & [1 - P_{n-3} + Q_{n-3}] \nu_{n-3} & [P_{n-2} - Q_{n-2}] \nu_{n-2} & 0 \\ \dots & 0 & [1 - P_{n-2} + Q_{n-2}] \nu_{n-2} & 0 \end{pmatrix}.
\end{aligned}$$

Obviously we have from (1.2) and the definitions of $\|\cdot\|_1$, $\|\cdot\|_2$, and $\|\cdot\|_3$ that

$$\begin{aligned} \|F(t, x(t), x(t-\tau))\|_2 &\leq \|A\|_3 |x|_1 \\ &\leq \sum_{i=0}^{n-2} [\bar{\nu}_i(\bar{P}_i + \bar{Q}_i) + \bar{\nu}_i(1 + \bar{P}_i + \bar{Q}_i)] |x|_1 \\ &= \left[\sum_{i=0}^{n-2} [\bar{\nu}_i(1 + 2\bar{P}_i + 2\bar{Q}_i)] \right] |x|_1. \end{aligned} \quad (3.3)$$

This implies that $F(t, x(t), x(t-\tau))$ satisfies the Lipschitzian condition in $x(t)$. Thus there exists a unique solution of Equation (1.1) by Theorem A.

Remark 3.2. There also exists a unique solution of Equation (1.1) when the time delay is $\tau = 0$.

2.4 STABILITY OF SOLUTIONS FOR NON-LINEAR GROWTH KINETICS OF BREAST CANCER STEM CELLS

Theorem 4.1. The solution $x = 0$ of Equation (1.1) is uniformly asymptotically stable if

$$\begin{aligned} (1 + 2\bar{P}_0 + \bar{Q}_0)\bar{\nu}_0 &\leq 2d_0, \\ (1 + \bar{Q}_0)\bar{\nu}_0 + (1 + 2\bar{P}_1 + \bar{Q}_1)\bar{\nu}_1 &\leq 2d_1, \\ &\vdots \\ (1 + \bar{Q}_{n-3})\bar{\nu}_{n-3} + (1 + 2\bar{P}_{n-2} + \bar{Q}_{n-2})\bar{\nu}_{n-2} &\leq 2d_{n-2}, \\ (1 + \bar{Q}_{n-2})\bar{\nu}_{n-2} &\leq 2d_{n-1}. \end{aligned}$$

Proof: Let

$$V(t, x(t)) = \frac{1}{2}(x_0^2(t) + x_1^2(t) + \cdots + x_{n-1}^2(t)). \quad (4.1)$$

Then

$$\mu(|x|_1) \leq V(t, x) \leq \nu(\|x\|_2)$$

with, for example, $\mu(s) = \frac{1}{2n}s^2$ and $\nu(s) = s^2$. We have from (1.1), (1.2), and (4.1) that

$$\begin{aligned}
V' &= [x_0(t)x_0'(t) + x_1(t)x_1'(t) + \cdots + x_{n-1}(t)x_{n-1}'(t)] \tag{4.2} \\
&= [P_0(x_{n-1}(t-\tau)) - Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0^2(t) - d_0x_0^2(t) \\
&\quad + [1 - P_0(x_{n-1}(t-\tau)) + Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t)x_1(t) \\
&\quad + [P_1(x_{n-1}(t-\tau)) - Q_1(x_{n-1}(t-\tau))]\nu_1(x_{n-1}(t-\tau))x_1^2(t) - d_1x_1^2(t) + \cdots \\
&\quad + [1 - P_{n-3}(x_{n-1}(t-\tau)) + Q_{n-3}(x_{n-1}(t-\tau))]\nu_{n-3}(x_{n-1}(t-\tau))x_{n-3}(t)x_{n-2}(t) \\
&\quad + [P_{n-2}(x_{n-1}(t-\tau)) - Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}^2(t) \\
&\quad - d_{n-2}x_{n-2}^2(t) + [1 - P_{n-2}(x_{n-1}(t-\tau)) + Q_{n-2}(x_{n-1}(t-\tau))] \\
&\quad \times \nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}(t)x_{n-1}(t) - d_{n-1}x_{n-1}^2(t) \\
&\leq \{[P_0(x_{n-1}(t-\tau)) - Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau)) - d_0 \\
&\quad + \frac{1}{2}[1 - P_0(x_{n-1}(t-\tau)) + Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))\}x_0^2(t) \\
&\quad + \{\frac{1}{2}[1 - P_0(x_{n-1}(t-\tau)) + Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau)) - d_1 \\
&\quad + [P_1(x_{n-1}(t-\tau)) - Q_1(x_{n-1}(t-\tau))]\nu_1(x_{n-1}(t-\tau)) \\
&\quad + \frac{1}{2}[1 - P_1(x_{n-1}(t-\tau)) + Q_1(x_{n-1}(t-\tau))]\nu_1(x_{n-1}(t-\tau))\}x_1^2(t) + \cdots \\
&\quad + \{\frac{1}{2}[1 - P_{n-3}(x_{n-1}(t-\tau)) + Q_{n-3}(x_{n-1}(t-\tau))]\nu_{n-3}(x_{n-1}(t-\tau)) - d_{n-2} \\
&\quad + [P_{n-2}(x_{n-1}(t-\tau)) - Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau)) \\
&\quad + \frac{1}{2}[1 - P_{n-2}(x_{n-1}(t-\tau)) + Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau))\}x_{n-2}^2(t) \\
&\quad + \{\frac{1}{2}[1 - P_{n-2}(x_{n-1}(t-\tau)) + Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau)) \\
&\quad - d_{n-1}\}x_{n-1}^2(t)
\end{aligned}$$

$$\begin{aligned}
&\leq \{\bar{P}_0\bar{\nu}_0 + \frac{1}{2}||[1 + \bar{Q}_0]\bar{\nu}_0| - d_0\}x_0^2(t) \\
&+ \{\frac{1}{2}||[1 + \bar{Q}_0]\bar{\nu}_0| + \bar{P}_1\bar{\nu}_1 + \frac{1}{2}||[1 + \bar{Q}_1]\bar{\nu}_1| - d_1\}x_1^2(t) + \dots \\
&+ \{\frac{1}{2}||[1 + \bar{Q}_{n-3}]\bar{\nu}_{n-3}| + \bar{P}_{n-2}\bar{\nu}_{n-2} + \frac{1}{2}||[1 + \bar{Q}_{n-2}]\bar{\nu}_{n-2}| - d_{n-2}\}x_{n-2}^2(t) \\
&+ \{\frac{1}{2}||[1 + \bar{Q}_{n-2}]\bar{\nu}_{n-2}| - d_{n-1}\}x_{n-1}^2(t).
\end{aligned}$$

Then the solution $x = 0$ of Equation (1.1) is uniformly asymptotically stable by Theorem B if

$$\begin{aligned}
&\bar{P}_0\bar{\nu}_0 + \frac{1}{2}||[1 + \bar{Q}_0]\bar{\nu}_0| - d_0 \leq 0, \\
&\frac{1}{2}||[1 + \bar{Q}_0]\bar{\nu}_0| + \bar{P}_1\bar{\nu}_1 + \frac{1}{2}||[1 + \bar{Q}_1]\bar{\nu}_1| - d_1 \leq 0, \\
&\vdots \\
&\frac{1}{2}||[1 + \bar{Q}_{n-3}]\bar{\nu}_{n-3}| + \bar{P}_{n-2}\bar{\nu}_{n-2} + \frac{1}{2}||[1 + \bar{Q}_{n-2}]\bar{\nu}_{n-2}| - d_{n-2} \leq 0, \\
&\frac{1}{2}||[1 + \bar{Q}_{n-2}]\bar{\nu}_{n-2}| - d_{n-1} \leq 0,
\end{aligned} \tag{4.3}$$

which implies

$$\begin{aligned}
&(1 + 2\bar{P}_0 + \bar{Q}_0)\bar{\nu}_0 \leq 2d_0, \\
&(1 + \bar{Q}_0)\bar{\nu}_0 + (1 + 2\bar{P}_1 + \bar{Q}_1)\bar{\nu}_1 \leq 2d_1, \\
&\vdots \\
&(1 + \bar{Q}_{n-3})\bar{\nu}_{n-3} + (1 + 2\bar{P}_{n-2} + \bar{Q}_{n-2})\bar{\nu}_{n-2} \leq 2d_{n-2}, \\
&(1 + \bar{Q}_{n-2})\bar{\nu}_{n-2} \leq 2d_{n-1}.
\end{aligned} \tag{4.4}$$

Remark 4.2. Theorem 4.1 still holds when $\tau = 0$.

We have another uniform asymptotic stability theorem about Equation (1.1) by using the method of characteristic equation when $\tau = 0$.

Theorem 4.3. Suppose $(x_0^*, x_1^* \dots, x_{n-1}^*)$ is a steady state solution of Equation (1.1) with $\tau = 0$. Then this steady state solution is uniformly asymptotically stable

if the roots of the characteristic equation

$$\det[\lambda I - A] = 0$$

satisfy $Re\lambda < 0$, where

$$A = \begin{pmatrix} a_{1,1} & 0 & 0 & \cdots & 0 & a_{1,n} \\ a_{2,1} & a_{2,2} & 0 & \cdots & 0 & a_{2,n} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & a_{n-1,n-1} & a_{n-1,n} \\ 0 & 0 & 0 & \cdots & a_{n,n-1} & a_{n,n} \end{pmatrix},$$

$$a_{1,1} = 0,$$

$$a_{2,1} = \nu_0(x_{n-1}^*)[1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*)],$$

$$a_{2,2} = [P_1(x_{n-1}^*) - Q_1(x_{n-1}^*)]\nu_1(x_{n-1}^*) - d_1,$$

$$\vdots$$

$$a_{n-1,n-2} = \nu_{n-3}(x_{n-1}^*)[1 - P_{n-3}(x_{n-1}^*) + Q_{n-3}(x_{n-1}^*)],$$

$$a_{n-1,n-1} = [P_{n-2}(x_{n-1}^*) - Q_{n-2}(x_{n-1}^*)]\nu_{n-2}(x_{n-1}^*) - d_{n-2},$$

$$a_{n,n-1} = \nu_{n-2}(x_{n-1}^*)[1 - P_{n-2}(x_{n-1}^*) + Q_{n-2}(x_{n-1}^*)],$$

and

$$a_{1,n} = x_0^*[(P_0'(x_{n-1}^*) - Q_0'(x_{n-1}^*))\nu_0(x_{n-1}^*) + (P_0(x_{n-1}^*) - Q_0(x_{n-1}^*))\nu_0'(x_{n-1}^*)],$$

$$a_{2,n} = x_0^*[(-P_0'(x_{n-1}^*) + Q_0'(x_{n-1}^*))\nu_0(x_{n-1}^*)$$

$$+ (1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*))\nu_0'(x_{n-1}^*)]$$

$$+ x_1^*[(P_1'(x_{n-1}^*) - Q_1'(x_{n-1}^*))\nu_1(x_{n-1}^*) + (P_1(x_{n-1}^*) - Q_1(x_{n-1}^*))\nu_1'(x_{n-1}^*)],$$

$$\vdots$$

$$a_{n-1,n} = x_{n-3}^*[(-P_{n-3}'(x_{n-1}^*) + Q_{n-3}'(x_{n-1}^*))\nu_{n-3}(x_{n-1}^*) + (1 - P_{n-3}(x_{n-1}^*)$$

$$+ Q_{n-3}(x_{n-1}^*))\nu_{n-3}'(x_{n-1}^*)] + x_{n-2}^*[(P_{n-2}'(x_{n-1}^*) - Q_{n-2}'(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*)$$

$$\begin{aligned}
& + (P_{n-2}(x_{n-1}^*) - Q_{n-2}(x_{n-1}^*))\nu'_{n-2}(x_{n-1}^*), \\
a_{n,n} = & -d_{n-1} + x_{n-2}^* [(-P'_{n-2}(x_{n-1}^*) + Q'_{n-2}(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*) \\
& + (1 - P_{n-2}(x_{n-1}^*) + Q_{n-2}(x_{n-1}^*))\nu'_{n-2}(x_{n-1}^*)].
\end{aligned}$$

Proof: By linearization techniques, we have linear equation from (1.1)

$$\begin{aligned}
\frac{dx_0(t)}{dt} &= x_0^* \{ [P'_0(x_{n-1}^*) - Q'_0(x_{n-1}^*)]\nu_0(x_{n-1}^*) + [P_0(x_{n-1}^*) \\
& - Q_0(x_{n-1}^*)]\nu'_0(x_{n-1}^*) \} x_{n-1}(t), \\
\frac{dx_1(t)}{dt} &= \nu_0(x_{n-1}^*) [1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*)] x_0(t) + \{ [P_1(x_{n-1}^*) \\
& - Q_1(x_{n-1}^*)]\nu_1(x_{n-1}^*) - d_1 \} x_1(t) + \{ x_0^* [(-P'_0(x_{n-1}^*) \\
& + Q'_0(x_{n-1}^*))\nu_0(x_{n-1}^*) + (1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*))\nu'_0(x_{n-1}^*)] \\
& + x_1^* [(P'_1(x_{n-1}^*) - Q'_1(x_{n-1}^*))\nu_1(x_{n-1}^*) + (P_1(x_{n-1}^*) \\
& - Q_1(x_{n-1}^*))\nu'_1(x_{n-1}^*)] \} x_{n-1}(t), \\
& \vdots \\
\frac{dx_{n-2}(t)}{dt} &= \nu_{n-3}(x_{n-1}^*) [1 - P_{n-3}(x_{n-1}^*) + Q_{n-3}(x_{n-1}^*)] x_{n-3}(t) + \{ [P_{n-2}(x_{n-1}^*) \\
& - Q_{n-2}(x_{n-1}^*)]\nu_{n-2}(x_{n-1}^*) - d_{n-2} \} x_{n-2}(t) + \{ x_{n-3}^* [(-P'_{n-3}(x_{n-1}^*) \\
& + Q'_{n-3}(x_{n-1}^*))\nu_{n-3}(x_{n-1}^*) + (1 - P_{n-3}(x_{n-1}^*) + Q_{n-3}(x_{n-1}^*))\nu'_{n-3}(x_{n-1}^*)] \\
& + x_{n-2}^* [(P'_{n-2}(x_{n-1}^*) - Q'_{n-2}(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*) + (P_{n-2}(x_{n-1}^*) \\
& - Q_{n-2}(x_{n-1}^*))\nu'_{n-2}(x_{n-1}^*)] \} x_{n-1}(t), \\
\frac{dx_{n-1}(t)}{dt} &= \nu_{n-2}(x_{n-1}^*) [1 - P_{n-2}(x_{n-1}^*) + Q_{n-2}(x_{n-1}^*)] x_{n-2}(t) + \{ -d_{n-1} \\
& + x_{n-2}^* [(-P'_{n-2}(x_{n-1}^*) + Q'_{n-2}(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*) + (1 - P_{n-2}(x_{n-1}^*) \\
& + Q_{n-2}(x_{n-1}^*))\nu'_{n-2}(x_{n-1}^*)] \} x_{n-1}(t).
\end{aligned} \tag{4.5}$$

We have from (4.5) that

$$\dot{X}(t) = AX(t). \tag{4.6}$$

Therefore the steady state solution $(x_0^*, x_1^*, \dots, x_1^*)$ of Equation (1.1) with $\tau = 0$ is uniformly asymptotically stable if the roots of the characteristic equation

$$\det[\lambda I - A] = 0 \quad (4.7)$$

satisfy $\operatorname{Re} \lambda < 0$.

Theorem 4.4. Suppose $(x_0^*, x_1^*, \dots, x_{n-1}^*)$ is a steady state solution of Equation (1.1). Then this steady state solution is uniformly asymptotically stable if the roots of the characteristic equation

$$\det[\lambda I - A - B e^{-\lambda \tau}] = 0$$

satisfy $\operatorname{Re} \lambda < 0$, where

$$A = \begin{pmatrix} a_{11} & 0 & 0 & \cdots & 0 & 0 \\ a_{21} & a_{22} & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & a_{n-1,n-1} & 0 \\ 0 & 0 & 0 & \cdots & a_{n,n-1} & a_{n,n} \end{pmatrix},$$

$$B = \begin{pmatrix} 0 & 0 & \cdots & 0 & b_{1n} \\ 0 & 0 & \cdots & 0 & b_{2n} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 0 & b_{nn} \end{pmatrix},$$

$$a_{11} = 0,$$

$$a_{2,1} = \nu_0(x_{n-1}^*)[1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*)],$$

$$a_{2,2} = [P_1(x_{n-1}^*) - Q_1(x_{n-1}^*)]\nu_1(x_{n-1}^*) - d_1,$$

$$\vdots$$

$$a_{n-1,n-2} = \nu_{n-3}(x_{n-1}^*)[1 - P_{n-3}(x_{n-1}^*) + Q_{n-3}(x_{n-1}^*)],$$

$$a_{n-1,n-1} = [P_{n-2}(x_{n-1}^*) - Q_{n-2}(x_{n-1}^*)]\nu_{n-2}(x_{n-1}^*) - d_{n-2},$$

$$a_{n,n-1} = \nu_{n-2}(x_{n-1}^*)[1 - P_{n-2}(x_{n-1}^*) + Q_{n-2}(x_{n-1}^*)],$$

$$a_{n,n} = -d_{n-1},$$

$$b_{1,n} = x_0^*[(P_0'(x_{n-1}^*) - Q_0'(x_{n-1}^*))\nu_0(x_{n-1}^*) + (P_0(x_{n-1}^*) - Q_0(x_{n-1}^*))\nu_0'(x_{n-1}^*)],$$

$$b_{2,n} = x_0^*[(-P_0'(x_{n-1}^*) + Q_0'(x_{n-1}^*))\nu_0(x_{n-1}^*)$$

$$+ (1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*))\nu_0'(x_{n-1}^*)]$$

$$+ x_1^*[(P_1'(x_{n-1}^*) - Q_1'(x_{n-1}^*))\nu_1(x_{n-1}^*) + (P_1(x_{n-1}^*) - Q_1(x_{n-1}^*))\nu_1'(x_{n-1}^*)],$$

⋮

$$b_{n-1,n} = x_{n-3}^*[(-P_{n-3}'(x_{n-1}^*) + Q_{n-3}'(x_{n-1}^*))\nu_{n-3}(x_{n-1}^*) + (1 - P_{n-3}(x_{n-1}^*)$$

$$+ Q_{n-3}(x_{n-1}^*))\nu_{n-3}'(x_{n-1}^*)] + x_{n-2}^*[(P_{n-2}'(x_{n-1}^*) - Q_{n-2}'(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*)$$

$$+ (P_{n-2}(x_{n-1}^*) - Q_{n-2}(x_{n-1}^*))\nu_{n-2}'(x_{n-1}^*)],$$

$$b_{n,n} = x_{n-2}^*[(-P_{n-2}'(x_{n-1}^*) + Q_{n-2}'(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*) + (1 - P_{n-2}(x_{n-1}^*)$$

$$+ Q_{n-2}(x_{n-1}^*))\nu_{n-2}'(x_{n-1}^*)].$$

Proof: By linearization techniques, we have the linear equation from (1.1)

$$\frac{dx_0(t)}{dt} = x_0^*\{[P_0'(x_{n-1}^*) - Q_0'(x_{n-1}^*)]\nu_0(x_{n-1}^*) + [P_0(x_{n-1}^*)$$

$$- Q_0(x_{n-1}^*)]\nu_0'(x_{n-1}^*)\}x_{n-1}(t - \tau),$$

$$\frac{dx_1(t)}{dt} = \nu_0(x_{n-1}^*)[1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*)]x_0(t) + \{[P_1(x_{n-1}^*) -$$

$$Q_1(x_{n-1}^*)]\nu_1(x_{n-1}^*) - d_1\}x_1(t) + \{x_0^*[(-P_0'(x_{n-1}^*) + Q_0'(x_{n-1}^*))\nu_0(x_{n-1}^*) +$$

$$(1 - P_0(x_{n-1}^*) + Q_0(x_{n-1}^*))\nu_0'(x_{n-1}^*)] + x_1^*[(P_1'(x_{n-1}^*) - Q_1'(x_{n-1}^*))\nu_1(x_{n-1}^*)$$

$$+ (P_1(x_{n-1}^*) - Q_1(x_{n-1}^*))\nu_1'(x_{n-1}^*)]\}x_{n-1}(t - \tau),$$

⋮

$$\frac{dx_{n-2}(t)}{dt} = \nu_{n-3}(x_{n-1}^*)[1 - P_{n-3}(x_{n-1}^*) + Q_{n-3}(x_{n-1}^*)]x_{n-3}(t) + \{[P_{n-2}(x_{n-1}^*)$$

$$- Q_{n-2}(x_{n-1}^*)]\nu_{n-2}(x_{n-1}^*) - d_{n-2}\}x_{n-2}(t) + \{x_{n-3}^*[(-P_{n-3}'(x_{n-1}^*)$$

$$\begin{aligned}
& + Q'_{n-3}(x_{n-1}^*)\nu_{n-3}(x_{n-1}^*) + (1 - P_{n-3}(x_{n-1}^*) + Q_{n-3}(x_{n-1}^*))\nu'_{n-3}(x_{n-1}^*)] \\
& + x_{n-2}^*[(P'_{n-2}(x_{n-1}^*) - Q'_{n-2}(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*) + (P_{n-2}(x_{n-1}^*) \\
& - Q_{n-2}(x_{n-1}^*))\nu'_{n-2}(x_{n-1}^*)]x_{n-1}(t - \tau), \\
\frac{dx_{n-1}(t)}{dt} & = \nu_{n-2}(x_{n-1}^*)[1 - P_{n-2}(x_{n-1}^*) + Q_{n-2}(x_{n-1}^*)]x_{n-2}(t) - d_{n-1}x_{n-1}(t) \\
& + x_{n-2}^*[(-P'_{n-2}(x_{n-1}^*) + Q'_{n-2}(x_{n-1}^*))\nu_{n-2}(x_{n-1}^*) + (1 - P_{n-2}(x_{n-1}^*) \\
& + Q_{n-2}(x_{n-1}^*))\nu'_{n-2}(x_{n-1}^*)]x_{n-1}(t - \tau),
\end{aligned}$$

where $(x_0^*, x_1^*, \dots, x_{n-1}^*)$ is a steady state solution of Equation (1.1).

We have from (4.8) that

$$\dot{X}(t) = AX(t) + BX(t - \tau).$$

Therefore the steady state solution $(x_0^*, x_1^*, \dots, x_{n-1}^*)$ of Equation (1.1) is uniformly asymptotically stable if the roots of the characteristic equation

$$\det[\lambda I - A - Be^{-\lambda\tau}] = 0 \quad (4.9)$$

satisfy $Re\lambda < 0$.

In order to guarantee that the roots of the characteristic equation (4.9) are in the left half-plane, the following result in [41] will be applied.

Theorem 4.5. Let $\Delta(z) = P(z, e^z)$ where $P(z, w)$ is a polynomial with principal term. Suppose $\Delta(iy)$, $y \in R$, is separated into its real and imaginary parts, $\Delta(iy) = F(y) + iG(y)$. If all zeros of $\Delta(z)$ have negative real parts, then the zeros of $F(y)$ and $G(y)$ are real, simple, and alternate and

$$G'(y)F(y) - G(y)F'(y) > 0 \quad \text{for } y \in R. \quad (4.10)$$

Conversely, all zeros of $\Delta(z)$ will be in the left half-plane provided that either of the following conditions is satisfied:

(i) All the zeros of $F(y)$ and $G(y)$ are real, simple, and alternate and Inequality

(4.10) is satisfied for at least one y .

(ii) All the zeros of $F(y)$ are real and, for each zero, Relation (4.10) is satisfied.

(iii) All the zeros of $G(y)$ are real and, for each zero, Relation (4.10) is satisfied.

Let

$$\Delta(\lambda) = \det[\lambda I - A - Be^{-\lambda\tau}]. \quad (4.11)$$

Therefore we have:

Theorem 4.6. Suppose $(x_0^*, x_1^* \dots, x_{n-1}^*)$ is a steady state solution of Equation (1.1). Then this steady state solution is uniformly asymptotically stable if (4.11) satisfies either condition (i), (ii), or (iii) of Theorem 4.5.

2.5 EXAMPLES

We consider the following two special cases of (1.1)

$$\begin{aligned} \frac{dx_0(t)}{dt} &= \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) - d_0 x_0(t), \\ \frac{dx_2(t)}{dt} &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \\ &\quad - d_2 x_2(t), \end{aligned} \quad (5.1)$$

and

$$\begin{aligned} \frac{dx_0(t)}{dt} &= \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) - d_0 x_0(t), \\ \frac{dx_1(t)}{dt} &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \\ &\quad + \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} - \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t) \\ &\quad - d_1 x_1(t), \\ \frac{dx_2(t)}{dt} &= \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t) \\ &\quad - d_2 x_2(t). \end{aligned} \quad (5.2)$$

Theorem 5.1. Suppose Ω is an open set in $R \times C$, $p_0 \geq 0$, $q_0 \geq 0$, $\gamma_1^0 \geq 0$, $\gamma_2^0 \geq 0$, $\nu_0 \geq 0$, and $\beta_0 \geq 0$. If $(t, \phi) \in \Omega$, then there is a unique solution of Equation (5.1) through (t, ϕ) .

Proof. Firstly, we have from (5.1) that

$$\dot{x}(t) = -Dx(t) + F(t, x(t), x(t - \tau)) \quad (5.3)$$

with the initial condition

$$x(s) = \phi(s) \in C([- \tau, 0]; R^2), \quad -\tau \leq s \leq 0, \quad (5.4)$$

where $x(t) = (x_0(t), x_2(t))^T$, $D = \text{diag}(d_0, d_2)$,

$$\begin{aligned} F(t, x(t), x(t - \tau)) &= \begin{pmatrix} f_1 \\ f_2 \end{pmatrix} = A(x_2(t - \tau)) \begin{pmatrix} x_0 \\ x_2 \end{pmatrix} \\ &= \begin{pmatrix} \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \\ \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \end{pmatrix} \end{aligned}$$

and

$$A(x_2(t - \tau)) = \begin{pmatrix} \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} & 0 \\ \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} & 0 \end{pmatrix}.$$

Obviously we have that

$$\|F(t, x(t), x(t - \tau))\|_2 \leq \|A\|_3 |x|_1 \leq (\nu_0(1 + 2p_0 + 2q_0)) |x|_1. \quad (5.5)$$

This implies that $F(t, x(t), x(t - \tau))$ satisfies the Lipschitzian condition in $x(t)$. Thus there exists a unique solution of Equation (5.1) by Theorem A.

Remark 5.2. There also exists a unique solution of Equation (5.1) when the time delay is $\tau = 0$.

Remark 5.3. Obviously, $P_0(x_2) = \frac{p_0}{1 + \gamma_1^0(x_2)^2}$, $Q_0(x_2) = \frac{q_0}{1 + \gamma_2^0(x_2)^2}$, and $\nu_0(x_2) = \frac{\nu_0}{1 + \beta_0(x_2)^2}$ are decreasing functions of x_2 .

Theorem 5.4. Suppose Ω is an open set in $R \times C$, $p_j \geq 0$, $q_j \geq 0$, $\beta_j \geq 0$, $\nu_j \geq 0$, and $\gamma_i^j \geq 0$ ($i = 1, 2, j = 0, 1$). If $(t, \phi) \in \Omega$, then there is a unique solution of Equation (5.2) through (t, ϕ) .

Proof. Similar to (5.3) and (5.4), we have

$$\dot{x}(t) = -Dx(t) + F(t, x(t), x(t - \tau)) \quad (5.6)$$

with the initial condition

$$x(s) = \phi(s) \in C([- \tau, 0]; R^3), \quad -\tau \leq s \leq 0, \quad (5.7)$$

where $x(t) = (x_0(t), x_1(t), x_2(t))^T$, $D = \text{diag}(d_0, d_1, d_2)$,

$$F(t, x(t), x(t - \tau)) = \begin{pmatrix} f_1 \\ f_2 \\ f_3 \end{pmatrix} = A(x_2(t - \tau)) \begin{pmatrix} x_0 \\ x_1 \\ x_2 \end{pmatrix}$$

$$= \begin{pmatrix} \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \\ \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) + \\ \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} - \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t) \\ \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t), \end{pmatrix}$$

$$A(x_2) = \begin{pmatrix} [P_0(x_2) - Q_0(x_2)]\nu_0(x_2) & 0 & 0 \\ [1 - P_0(x_2) + Q_0(x_2)]\nu_0(x_2) & [P_1(x_2) - Q_1(x_2)]\nu_1(x_2) & 0 \\ 0 & [1 - P_1(x_2) + Q_1(x_2)]\nu_1(x_2) & 0 \end{pmatrix},$$

$$P_i(x_2) = \frac{p_i}{1 + \gamma_1^i(x_2)^2}, \quad Q_i(x_2) = \frac{q_i}{1 + \gamma_2^i(x_2)^2}, \quad \text{and } \nu_i(x_2) = \frac{\nu_i}{1 + \beta_i(x_2)^2} \quad (i = 0, 1).$$

Obviously we have that

$$\|F(t, x(t), x(t - \tau))\|_2 \leq \|A\|_3 |x|_1 \leq [\nu_0(1 + 2p_0 + 2q_0) + \nu_1(1 + 2p_1 + 2q_1)] |x|_1. \quad (5.8)$$

This implies that $F(t, x(t), x(t - \tau))$ satisfies the Lipschitzian condition in $x(t)$. Thus there exists a unique solution of Equation (5.2) by Theorem A.

Remark 5.5. There also exists a unique solution of Equation (5.2) when the time delay is $\tau = 0$.

Remark 5.6. Obviously, $P_i(x_2) = \frac{p_i}{1+\gamma_1^i(x_2)^2}$, $Q_i(x_2) = \frac{q_i}{1+\gamma_2^i(x_2)^2}$, and $\nu_i(x_2) = \frac{\nu_i}{1+\beta_i(x_2)^2}$ ($i = 0, 1$) are decreasing functions of x_2 .

Theorem 5.7. Suppose $(1 + 2p_0 + q_0)\nu_0 \leq 2d_0$ and $(1 + q_0)\nu_0 \leq 2d_2$. Then the solution $x = 0$ of Equation (5.1) is uniformly asymptotically stable.

Proof. Let

$$V(t, x(t)) = \frac{1}{2}(x_0^2(t) + x_2^2(t)). \quad (5.9)$$

Then

$$\begin{aligned} V' &= \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0^2(t) \\ &\quad - d_0 x_0^2(t) - d_2 x_2^2(t) \\ &\quad + \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) x_2(t) \\ &\leq \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0^2(t) \\ &\quad - d_0 x_0^2(t) - d_2 x_2^2(t) \\ &\quad + \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| \frac{x_0^2(t) + x_2^2(t)}{2} \\ &= \left\{ \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} - d_0 \right. \\ &\quad + \frac{1}{2} \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| \} x_0^2(t) \\ &\quad + \left\{ \frac{1}{2} \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| - d_2 \right\} x_2^2(t). \end{aligned} \quad (5.10)$$

Then the solution $x = 0$ of Equation (5.1) is uniformly asymptotically stable by Theorem B if

$$\begin{aligned} &\left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} - d_0 \\ &+ \frac{1}{2} \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| \leq 0, \end{aligned}$$

$$\frac{1}{2} \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| - d_2 \leq 0. \quad (5.11)$$

Then a sufficient condition can be taken,

$$\begin{aligned} (1 + 2p_0 + q_0)\nu_0 &\leq 2d_0, \\ (1 + q_0)\nu_0 &\leq 2d_2. \end{aligned} \quad (5.12)$$

Remark 5.8. Theorem 5.7 still holds when $\tau = 0$.

Remark 5.9. Obviously, Theorem 5.7 is a special case of Theorem 4.1.

We have another uniform asymptotic stability theorem about Equation (5.1) by using the method of characteristic equation when $\tau = 0$ as the following.

Theorem 5.10. Suppose (x_0^*, x_2^*) is a steady state solution of Equation (1.1) with $\tau = 0$. Then this steady state solution is uniformly asymptotically stable if

$$\begin{aligned} &-d_2 + x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{(1 + \gamma_1^0(x_2^*)^2)^2} - \frac{2q_0\gamma_2^0}{(1 + \gamma_2^0(x_2^*)^2)^2} \right] \right. \\ &\quad \left. - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{(1 + \beta_0(x_2^*)^2)^2} \right\} < 0. \end{aligned}$$

and

$$\begin{aligned} &\left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \\ &\quad \times x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{(1 + \gamma_1^0(x_2^*)^2)^2} + \frac{2q_0\gamma_2^0}{(1 + \gamma_2^0(x_2^*)^2)^2} \right] \right. \\ &\quad \left. - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{(1 + \beta_0(x_2^*)^2)^2} \right\} > 0 \end{aligned}$$

Proof. By linearization techniques, we have linear equation from (1.1)

$$\begin{aligned} \frac{dx_0(t)}{dt} &= x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} \right. \right. \\ &\quad \left. \left. - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\} x_2(t), \\ \frac{dx_2(t)}{dt} &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2} x_0(t) - d_2 x_2(t) + x_0^* x_2^* \end{aligned}$$

$$\begin{aligned} & \times \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} \right. \right. \\ & \left. \left. + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\} x_2(t), \end{aligned} \quad (5.13)$$

where (x_0^*, x_2^*) is a steady state solution of Equation (5.1) with $\tau = 0$.

We have from (5.13) that

$$\dot{X}(t) = AX(t), \quad (5.14)$$

where

$$A = \begin{pmatrix} a_1 & a_2 \\ a_3 & a_4 \end{pmatrix},$$

$$a_1 = 0,$$

$$\begin{aligned} a_2 &= x_0^*x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\ & \quad \left. - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\}, \\ a_3 &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2}, \\ a_4 &= x_0^*x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\ & \quad \left. - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\} - d_2. \end{aligned} \quad (5.15)$$

Therefore the steady state solution (x_0^*, x_2^*) of Equation (5.1) with $\tau = 0$ is uniformly asymptotically stable if the roots of the characteristic equation

$$\det[\lambda I - A] = \lambda^2 - (a_1 + a_4)\lambda + a_1a_4 - a_2a_3 = 0 \quad (5.16)$$

satisfy $Re\lambda < 0$.

Then we have from (5.14)–(5.16) that

$$-d_2 + x_0^*x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{(1 + \gamma_1^0(x_2^*)^2)^2} - \frac{2q_0\gamma_2^0}{(1 + \gamma_2^0(x_2^*)^2)^2} \right] \right.$$

$$- \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{(1 + \beta_0(x_2^*)^2)^2} \Big\} < 0.$$

and

$$\begin{aligned} & \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \\ & \times x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{(1 + \gamma_1^0(x_2^*)^2)^2} + \frac{2q_0\gamma_2^0}{(1 + \gamma_2^0(x_2^*)^2)^2} \right] \right. \\ & \left. - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{(1 + \beta_0(x_2^*)^2)^2} \right\} > 0 \end{aligned}$$

Theorem 5.11. The steady state solution of Equation (5.1) is uniformly asymptotically stable provided that

$$F(y) = -y^2 - a_4 y \sin y\tau + (a_1 a_4 - a_2 a_3) \cos y\tau - a_1 d_2$$

and

$$G(y) = y(d_2 - a_1 - a_4 \cos y\tau) + (a_2 a_3 - a_1 a_4) \sin y\tau$$

satisfy either condition (i), (ii), or (iii) of Theorem 4.4, where

$$\begin{aligned} a_1 &= 0 \\ a_2 &= x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\ & \quad \left. - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\}, \\ a_3 &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2}, \\ a_4 &= x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\ & \quad \left. - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\}. \end{aligned}$$

Proof. By linearization techniques, we have linear equation from (1.1)

$$\frac{dx_0(t)}{dt} = x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right.$$

$$\begin{aligned}
& - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \Big\} x_2(t - \tau) \\
\frac{dx_2(t)}{dt} = & \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2} x_0(t) - d_2 x_2(t) \\
& + x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\
& \left. - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\} x_2(t - \tau). \tag{5.19}
\end{aligned}$$

We have from (5.19) that

$$\dot{X}(t) = AX(t) + BX(t - \tau), \tag{5.20}$$

where

$$A = \begin{pmatrix} a_1 & 0 \\ a_3 & -d_2 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & a_2 \\ 0 & a_4 \end{pmatrix}. \tag{5.21}$$

Then we have the characteristic equation of Equation (5.1)

$$\det[\lambda I - A - Be^{-\lambda\tau}] = \lambda^2 + (d_2 - a_1 - a_4 e^{-\lambda\tau})\lambda - (d_2 - a_4 e^{-\lambda\tau})a_1 - a_2 a_3 e^{-\lambda\tau} = 0. \tag{5.22}$$

If $\Delta(\lambda) = \lambda^2 + (d_2 - a_1 - a_4 e^{-\lambda\tau})\lambda - (d_2 - a_4 e^{-\lambda\tau})a_1 - a_2 a_3 e^{-\lambda\tau}$, $\Delta(iy) = F(y) + iG(y)$, $y \in R$, then

$$F(y) = -y^2 - a_4 y \sin y\tau + (a_1 a_4 - a_2 a_3) \cos y\tau - a_1 d_2, \tag{5.23}$$

$$G(y) = y(d_2 - a_1 - a_4 \cos y\tau) + (a_2 a_3 - a_1 a_4) \sin y\tau.$$

By Theorem 4.4, the steady state solution of Equation (5.1) is uniformly asymptotically stable provided that equation (5.23) satisfies either condition (i), (ii), or (iii) of Theorem 4.5.

Theorem 5.12. Suppose $(1 + 2p_0 + q_0)\nu_0 \leq 2d_0$, $(1 + q_0)\nu_0 + (1 + 2p_1 + q_1)\nu_1 \leq 2d_1$, and $(1 + q_1)\nu_1 \leq 2d_2$. Then the solution $x = 0$ of Equation (5.2) is uniformly asymptotically stable.

Proof. Let

$$V(t, x(t)) = \frac{1}{2}(x_0^2(t) + x_1^2(t) + x_2^2(t)). \tag{5.24}$$

Then

$$\begin{aligned}
V' &= \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0^2(t) \\
&\quad - d_0 x_0^2(t) \\
&\quad + \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) x_1(t) \\
&\quad + \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} - \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1^2(t) \\
&\quad - d_1 x_1^2(t) \\
&\quad + \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t) x_2(t) \\
&\quad - d_2 x_2^2(t) \\
&\leq \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0^2(t) \\
&\quad - d_0 x_0^2(t) \\
&\quad + \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| \frac{x_0^2(t) + x_1^2(t)}{2} \\
&\quad + \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} - \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1^2(t) \\
&\quad - d_1 x_1^2(t) \\
&\quad + \left| \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} \right| \frac{x_1^2(t) + x_2^2(t)}{2} \\
&\quad - d_2 x_2^2(t) \\
&= \left\{ \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right. \\
&\quad \left. - d_0 \right. \\
&\quad \left. + \frac{1}{2} \left| \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right| \right\} x_0^2(t)
\end{aligned}$$

$$\begin{aligned}
& + \left\{ \frac{1}{2} \left| 1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right| \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} \right. \\
& + \left. \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} - \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} \right. \\
& - d_1 \\
& + \left. \frac{1}{2} \left| 1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right| \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} \right\} x_1^2(t) \\
& + \left\{ \frac{1}{2} \left| 1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right| \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} \right| - d_2 \} x_2^2(t)
\end{aligned} \tag{5.25}$$

Then the solution $x = 0$ of Equation (5.2) is uniformly asymptotically stable by Theorem B if

$$\begin{aligned}
& \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right. \\
& + \left. \frac{1}{2} \left| 1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right| \right] \\
& \quad \times \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} - d_0 \leq 0, \\
& \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} - \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right. \\
& + \left. \frac{1}{2} \left| 1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right| \right] \\
& \quad \times \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} \\
& + \frac{1}{2} \left| 1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right| \\
& \quad \times \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} - d_1 \leq 0, \\
& \frac{1}{2} \left| 1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right| \\
& \quad \times \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} - d_2 \leq 0.
\end{aligned} \tag{5.26}$$

Then a sufficient condition can be taken,

$$\begin{aligned}
(1 + 2p_0 + q_0)\nu_0 &\leq 2d_0, \\
(1 + q_0)\nu_0 + (1 + 2p_1 + q_1)\nu_1 &\leq 2d_1, \\
(1 + q_1)\nu_1 &\leq 2d_2.
\end{aligned} \tag{5.27}$$

Remark 5.13. Theorem 5.11 still holds when $\tau = 0$.

Remark 5.14. Obviously, Theorem 5.11 is a special case of Theorem 4.1.

Theorem 5.15. The steady state solution of Equation (5.2) is uniformly asymptotically stable provided that

$$\begin{aligned}
F(y) &= [(a_5 + a_3 + a_1) + b_3 \cos y\tau]y^2 + y(a_3b_3 - b_2a_4 + a_1b_3) \sin y\tau - a_1a_3a_5 \\
&\quad - [b_1a_2a_4 + a_1(a_3b_3 - b_2a_4)] \cos y\tau
\end{aligned}$$

and

$$\begin{aligned}
G(y) &= -y^3 - (b_3 \sin y\tau)y^2 + [a_3a_5 + a_1(a_5 + a_3) + (a_3b_3 - b_2a_4 + a_1b_3) \cos y\tau]y \\
&\quad + [b_1a_2a_4 + a_1(a_3b_3 - b_2a_4)] \sin y\tau.
\end{aligned}$$

satisfy either condition (i), (ii), or (iii) of Theorem 4.5, where

$$\begin{aligned}
a_1 &= 0, \\
a_2 &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2}\right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2}, \\
a_3 &= \left[\frac{p_1}{1 + \gamma_1^1(x_2^*)^2} - \frac{q_1}{1 + \gamma_2^1(x_2^*)^2}\right] \frac{\nu_1}{1 + \beta_1(x_2^*)^2} - d_1, \\
a_4 &= \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2^*)^2} + \frac{q_1}{1 + \gamma_2^1(x_2^*)^2}\right] \frac{\nu_1}{1 + \beta_1(x_2^*)^2}, \\
a_5 &= -d_2, \\
b_1 &= x_0^*x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\
&\quad \left. - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\},
\end{aligned}$$

$$\begin{aligned}
b_2 &= x_2^* \left\{ \frac{\nu_0 x_0^*}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0 \gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0 \gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\
&\quad - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \times \frac{2\nu_0 \beta_0 x_0^*}{[1 + \beta_0(x_2^*)^2]^2} \\
&\quad + \frac{\nu_1 x_1^*}{1 + \beta_1(x_2^*)^2} \left[-\frac{2p_1 \gamma_1^1}{[1 + \gamma_1^1(x_2^*)^2]^2} + \frac{2q_1 \gamma_2^1}{[1 + \gamma_2^1(x_2^*)^2]^2} \right] \\
&\quad \left. - \left[\frac{p_1}{1 + \gamma_1^1(x_2^*)^2} - \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \times \frac{2\nu_1 \beta_1 x_1^*}{[1 + \beta_1(x_2^*)^2]^2} \right\}, \\
b_3 &= x_1^* x_2^* \left\{ \frac{\nu_1}{1 + \beta_1(x_2^*)^2} \left[\frac{2p_1 \gamma_1^1}{[1 + \gamma_1^1(x_2^*)^2]^2} - \frac{2q_1 \gamma_2^1}{[1 + \gamma_2^1(x_2^*)^2]^2} \right] \right. \\
&\quad \left. - \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2^*)^2} + \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{2\nu_1 \beta_1}{[1 + \beta_1(x_2^*)^2]^2} \right\}.
\end{aligned}$$

Proof: By linearization techniques, we have linear equation from (5.2)

$$\begin{aligned}
\frac{dx_0(t)}{dt} &= x_0^* x_2^* \left\{ \frac{\nu_0}{1 + \beta_0(x_2^*)^2} \left[-\frac{2p_0 \gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} + \frac{2q_0 \gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\
&\quad \left. - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0 \beta_0}{[1 + \beta_0(x_2^*)^2]^2} \right\} x_2(t - \tau), \\
\frac{dx_1(t)}{dt} &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2} x_0(t) \\
&\quad + \left\{ \left[\frac{p_1}{1 + \gamma_1^1(x_2^*)^2} - \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{\nu_1}{1 + \beta_1(x_2^*)^2} - d_1 \right\} x_1(t) \\
&\quad + x_2^* \left\{ \frac{\nu_0 x_0^*}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0 \gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0 \gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\
&\quad - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0 \beta_0 x_0^*}{[1 + \beta_0(x_2^*)^2]^2} \\
&\quad + \frac{\nu_1 x_1^*}{1 + \beta_1(x_2^*)^2} \left[-\frac{2p_1 \gamma_1^1}{[1 + \gamma_1^1(x_2^*)^2]^2} + \frac{2q_1 \gamma_2^1}{[1 + \gamma_2^1(x_2^*)^2]^2} \right] \\
&\quad \left. - \left[\frac{p_1}{1 + \gamma_1^1(x_2^*)^2} - \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{2\nu_1 \beta_1 x_1^*}{[1 + \beta_1(x_2^*)^2]^2} \right\} x_2(t - \tau), \\
\frac{dx_2(t)}{dt} &= \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2^*)^2} + \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{\nu_1}{1 + \beta_1(x_2^*)^2} x_1(t) \\
&\quad + x_1^* x_2^* \left\{ \frac{\nu_1}{1 + \beta_1(x_2^*)^2} \left[\frac{2p_1 \gamma_1^1}{[1 + \gamma_1^1(x_2^*)^2]^2} - \frac{2q_1 \gamma_2^1}{[1 + \gamma_2^1(x_2^*)^2]^2} \right] \right.
\end{aligned}$$

$$- \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2^*)^2} + \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{2\nu_1\beta_1}{[1 + \beta_1(x_2^*)^2]^2} \} x_2(t - \tau) - d_2 x_2(t), \quad (5.28)$$

where (x_0^*, x_1^*, x_2^*) is a steady state solution of Equation (5.2). We have from (5.28) that

$$\dot{X}(t) = AX(t) + BX(t - \tau), \quad (5.29)$$

where

$$A = \begin{pmatrix} a_1 & 0 & 0 \\ a_2 & a_3 & 0 \\ 0 & a_4 & a_5 \end{pmatrix}, \quad B = \begin{pmatrix} 0 & 0 & b_1 \\ 0 & 0 & b_2 \\ 0 & 0 & b_3 \end{pmatrix}. \quad (5.30)$$

Then we have the characteristic equation of system (5.2)

$$\begin{aligned} \det[\lambda I - A - Be^{-\lambda\tau}] &= \lambda^3 - [(a_5 + a_3 + a_1) + b_3 e^{-\lambda\tau}] \lambda^2 \\ &\quad + [a_3 a_5 + a_1(a_5 + a_3) + (a_3 b_3 - b_2 a_4 + a_1 b_3) e^{-\lambda\tau}] \lambda \\ &\quad - a_1 a_3 a_5 - [b_1 a_2 a_4 + a_1(a_3 b_3 - b_2 a_4)] e^{-\lambda\tau} \\ &= 0. \end{aligned} \quad (5.31)$$

If

$$\begin{aligned} \Delta(\lambda) &= \lambda^3 - [(a_5 + a_3 + a_1) + b_3 e^{-\lambda\tau}] \lambda^2 + [a_3 a_5 + a_1(a_5 + a_3) + (a_3 b_3 - b_2 a_4 \\ &\quad + a_1 b_3) e^{-\lambda\tau}] \lambda - a_1 a_3 a_5 - [b_1 a_2 a_4 + a_1(a_3 b_3 - b_2 a_4)] e^{-\lambda\tau}, \end{aligned}$$

$\Delta(iy) = F(y) + iG(y)$, $y \in R$, then

$$\begin{aligned} F(y) &= [(a_5 + a_3 + a_1) + b_3 \cos y\tau] y^2 + y(a_3 b_3 - b_2 a_4 + a_1 b_3) \sin y\tau - a_1 a_3 a_5 \\ &\quad - [b_1 a_2 a_4 + a_1(a_3 b_3 - b_2 a_4)] \cos y\tau, \\ G(y) &= -y^3 - (b_3 \sin y\tau) y^2 + [a_3 a_5 + a_1(a_5 + a_3) + (a_3 b_3 - b_2 a_4 + a_1 b_3) \cos y\tau] y \\ &\quad + [b_1 a_2 a_4 + a_1(a_3 b_3 - b_2 a_4)] \sin y\tau. \end{aligned} \quad (5.32)$$

By Theorem 4.4, the steady state solution of Equation (5.2) is uniformly asymptotically stable provided that (5.32) satisfies either condition (i), (ii), or (iii) of Theorem

4.5.

Theorem 5.16. Suppose (x_0^*, x_1^*, x_2^*) is a steady state solution of Equation (5.2) with $\tau = 0$. Then this steady state solution is uniformly asymptotically stable if the roots of the characteristic equation

$$\det[\lambda I - A] = \lambda^3 - (a_3 + a_6)\lambda^2 + [a_3a_6 - a_4a_5]\lambda - a_1a_2a_5 = 0$$

satisfy $\text{Re}\lambda < 0$, where

$$\begin{aligned} a_1 &= x_0^*x_2^*\left\{\frac{\nu_0}{1+\beta_0(x_2^*)^2}\left[-\frac{2p_0\gamma_1^0}{[1+\gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1+\gamma_2^0(x_2^*)^2]^2}\right] \right. \\ &\quad \left. - \left[\frac{p_0}{1+\gamma_1^0(x_2^*)^2} - \frac{q_0}{1+\gamma_2^0(x_2^*)^2}\right]\frac{2\nu_0\beta_0}{[1+\beta_0(x_2^*)^2]^2}\right\}, \\ a_2 &= \left[1 - \frac{p_0}{1+\gamma_1^0(x_2^*)^2} + \frac{q_0}{1+\gamma_2^0(x_2^*)^2}\right]\frac{\nu_0}{1+\beta_0(x_2^*)^2}, \\ a_3 &= \left[\frac{p_1}{1+\gamma_1^1(x_2^*)^2} - \frac{q_1}{1+\gamma_2^1(x_2^*)^2}\right]\frac{\nu_1}{1+\beta_1(x_2^*)^2} - d_1, \\ a_4 &= x_2^*\left\{\frac{\nu_0x_0^*}{1+\beta_0(x_2^*)^2}\left[\frac{2p_0\gamma_1^0}{[1+\gamma_1^0(x_2^*)^2]^2} - \frac{2q_0\gamma_2^0}{[1+\gamma_2^0(x_2^*)^2]^2}\right] \right. \\ &\quad \left. - \left[1 - \frac{p_0}{1+\gamma_1^0(x_2^*)^2} + \frac{q_0}{1+\gamma_2^0(x_2^*)^2}\right]\frac{2\nu_0\beta_0x_0^*}{[1+\beta_0(x_2^*)^2]^2} \right. \\ &\quad \left. + \frac{\nu_1x_1^*}{1+\beta_1(x_2^*)^2}\left[-\frac{2p_1\gamma_1^1}{[1+\gamma_1^1(x_2^*)^2]^2} + \frac{2q_1\gamma_2^1}{[1+\gamma_2^1(x_2^*)^2]^2}\right] \right. \\ &\quad \left. - \left[\frac{p_1}{1+\gamma_1^1(x_2^*)^2} - \frac{q_1}{1+\gamma_2^1(x_2^*)^2}\right]\frac{2\nu_1\beta_1x_1^*}{[1+\beta_1(x_2^*)^2]^2}\right\} \\ a_5 &= \left[1 - \frac{p_1}{1+\gamma_1^1(x_2^*)^2} + \frac{q_1}{1+\gamma_2^1(x_2^*)^2}\right]\frac{\nu_1}{1+\beta_1(x_2^*)^2}, \\ a_6 &= x_1^*x_2^*\left\{\frac{\nu_1}{1+\beta_1(x_2^*)^2}\left[\frac{2p_1\gamma_1^1}{[1+\gamma_1^1(x_2^*)^2]^2} - \frac{2q_1\gamma_2^1}{[1+\gamma_2^1(x_2^*)^2]^2}\right] \right. \\ &\quad \left. - \left[1 - \frac{p_1}{1+\gamma_1^1(x_2^*)^2} + \frac{q_1}{1+\gamma_2^1(x_2^*)^2}\right]\frac{2\nu_1\beta_1}{[1+\beta_1(x_2^*)^2]^2}\right\} - d_2. \end{aligned}$$

Proof. If $\tau = 0$, We have from (5.28) that

$$\frac{dx_0(t)}{dt} = x_0^*x_2^*\left\{\frac{\nu_0}{1+\beta_0(x_2^*)^2}\left[-\frac{2p_0\gamma_1^0}{[1+\gamma_1^0(x_2^*)^2]^2} + \frac{2q_0\gamma_2^0}{[1+\gamma_2^0(x_2^*)^2]^2}\right]\right.$$

$$\begin{aligned}
& - \left[\frac{p_0}{1 + \gamma_1^0(x_2^*)^2} - \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0}{[1 + \beta_0(x_2^*)^2]^2} \} x_2(t), \\
\frac{dx_1(t)}{dt} = & \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{\nu_0}{1 + \beta_0(x_2^*)^2} x_0(t) \\
& + \left\{ \left[\frac{p_1}{1 + \gamma_1^1(x_2^*)^2} - \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{\nu_1}{1 + \beta_1(x_2^*)^2} - d_1 \right\} x_1(t) \\
& + x_2^* \left\{ \frac{\nu_0 x_0^*}{1 + \beta_0(x_2^*)^2} \left[\frac{2p_0\gamma_1^0}{[1 + \gamma_1^0(x_2^*)^2]^2} - \frac{2q_0\gamma_2^0}{[1 + \gamma_2^0(x_2^*)^2]^2} \right] \right. \\
& - \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2^*)^2} + \frac{q_0}{1 + \gamma_2^0(x_2^*)^2} \right] \frac{2\nu_0\beta_0 x_0^*}{[1 + \beta_0(x_2^*)^2]^2} \\
& + \frac{\nu_1 x_1^*}{1 + \beta_1(x_2^*)^2} \left[-\frac{2p_1\gamma_1^1}{[1 + \gamma_1^1(x_2^*)^2]^2} + \frac{2q_1\gamma_2^1}{[1 + \gamma_2^1(x_2^*)^2]^2} \right] \\
& \left. - \left[\frac{p_1}{1 + \gamma_1^1(x_2^*)^2} - \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{2\nu_1\beta_1 x_1^*}{[1 + \beta_1(x_2^*)^2]^2} \right\} x_2(t), \\
\frac{dx_2(t)}{dt} = & \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2^*)^2} + \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{\nu_1}{1 + \beta_1(x_2^*)^2} x_1(t) \\
& + x_1^* x_2^* \left\{ \frac{\nu_1}{1 + \beta_1(x_2^*)^2} \left[\frac{2p_1\gamma_1^1}{[1 + \gamma_1^1(x_2^*)^2]^2} - \frac{2q_1\gamma_2^1}{[1 + \gamma_2^1(x_2^*)^2]^2} \right] \right. \\
& \left. - \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2^*)^2} + \frac{q_1}{1 + \gamma_2^1(x_2^*)^2} \right] \frac{2\nu_1\beta_1}{[1 + \beta_1(x_2^*)^2]^2} \right\} x_2(t) - d_2 x_2(t). \quad (5.33)
\end{aligned}$$

We have from (5.33) that

$$\dot{X}(t) = AX(t), \quad (5.34)$$

where

$$A = \begin{pmatrix} 0 & 0 & a_1 \\ a_2 & a_3 & a_4 \\ 0 & a_5 & a_6 \end{pmatrix}, \quad \lambda I - A = \begin{pmatrix} \lambda & 0 & -a_1 \\ -a_2 & \lambda - a_3 & -a_4 \\ 0 & -a_5 & \lambda - a_6 \end{pmatrix}. \quad (5.35)$$

Then we have the characteristic equation of Equation (5.2)

$$\det[\lambda I - A] = \lambda^3 - (a_3 + a_6)\lambda^2 + [a_3a_6 - a_4a_5]\lambda - a_1a_2a_5 = 0. \quad (5.36)$$

Therefore the steady state solution (x_0^*, x_1^*, x_2^*) of Equation (5.2) with $\tau = 0$ is uniformly asymptotically stable if the roots of the characteristic equation (5.36) satisfy $Re\lambda < 0$.

2.6 NUMERICAL SIMULATIONS

We consider the following special case of (1.1) with three types of cells as presented in [37]

$$\begin{aligned}
\frac{dx_0}{dt} &= \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) - d_0 x_0(t), \\
\frac{dx_1}{dt} &= \left[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \\
&\quad + \left[\frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t) - d_1 x_1(t), \\
\frac{dx_2}{dt} &= \left[1 - \frac{p_1}{1 + \gamma_1^1(x_2(t - \tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t - \tau))^2} \right] \frac{\nu_1}{1 + \beta_1(x_2(t - \tau))^2} x_1(t) - d_2 x_2(t),
\end{aligned} \tag{6.1}$$

where $x_0(t)$, $x_1(t)$, and $x_2(t)$ are the number of cancer stem cells (CSCs), progenitor cells (PCs), and terminally differentiated cells (TDCs), respectively, at time t .

The figures show the solution of (6.1) implemented in MATLAB with initial condition $x(0) = (10, 200, 800)^T$. The parameters used in the figure are listed in Table (2.1). All of the figures have the same parameters and differ only in the time delay, τ . The time-delay is 0, 5, 10, and 20 time units for Figures (2.1)a, b, c, and d, respectively. The x -axis is time units, and the y -axis is number of cells in a log-scale. The inset shows a zoomed-in portion of the graph.

In Figure (2.1)a, the number of cells quickly grows to about 10^4 and then levels off. Stable equilibrium is reached. In Figure (2.1)b, the number of cells quickly grows to about 10^6 and then eventually levels off to the same level as Figure (2.1)a. Stable equilibrium is eventually reached. In Figure (2.1)c, we see similar behavior to Figure (2.1)b. Dynamic equilibrium is reached, but it is not stable since there are small oscillations in the number cells around the equilibrium position. In Figure (2.1)d, the number of cells quickly grows to about 10^6 and then levels off. This is two orders of magnitude greater than the previous scenarios. Dynamic equilibrium is reached, but

it is not stable since there are large oscillations in the number of all cell types around the equilibrium position. These results suggest that for a given set of parameters, the time delay disrupts the stability of the steady state solution, with greater time delays causing greater disruptions. This is reasonable since, from our analysis, the sufficient conditions for stability of the steady state solution for zero time delay, Theorem 5.16, vary from those for nonzero time delay, Theorem 5.15. In this case, the threshold where stability is disrupted is between $\tau = 5$ and $\tau = 10$.

The parameters were chosen both from biological data from our collaborator's lab [37] and from requiring that equilibrium is reached. From experiments with tumor cells we know that the degradation rate is the greatest for TDCs, then PCs, and then CSCs. We also know that the equilibrium tumor size is roughly 10^6 total cells. Additionally, the probabilities, p_0 , q_0 , p_1 , and q_1 , and degradation rates, d_0 , d_1 , and d_2 , are between 0 and 1 by definition. With these restrictions, the parameters were then chosen through guess and check until equilibrium was reached. The parameters for zero time delay satisfy the conditions of Theorem 5.16.

Table 2.1: Parameters used in Figures (2.1).

Parameter	Value	Parameter	Value	Parameter	Value
p_0	0.5	q_0	0.2	ν_0	10
p_1	0.001	q_1	0.9	ν_1	10
γ_1^0	7×10^{-9}	γ_2^0	4×10^{-10}	β_0	3×10^{-8}
γ_1^1	2×10^2	γ_2^1	8×10^{-18}	β_1	2×10^{-7}
d_0	0.001	d_1	0.08	d_2	0.085

2.7 CONCLUSION

Cancer stem cells are responsible for tumor survival and resurgence and are thus essential in developing novel therapeutic strategies against cancer. Mathematical modeling is employed to study the growth kinetics of breast CSCs. In this chapter, we have generalized a particular model that was used in [37] for non-linear growth

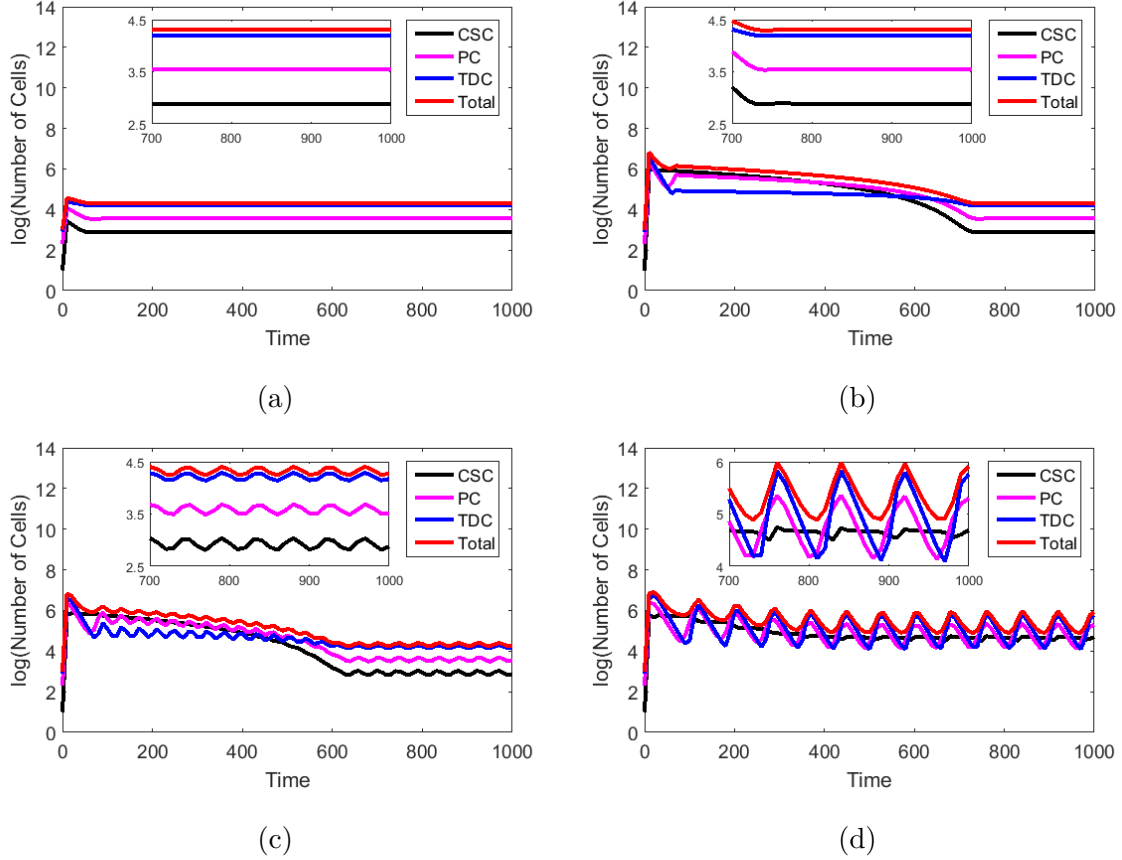


Figure 2.1: Solution of (6.1). Parameters are listed in Table (2.1). (a) $\tau = 0$. (b) $\tau = 5$. (c) $\tau = 10$. (d) $\tau = 20$.

kinetics of breast CSCs. By applying a theory from functional and ordinary differential equations, we proved the existence of unique solutions. By additionally applying a theorem from complex analysis and using linearization techniques, we have given a criteria for uniform asymptotic stability of the zero and steady state solutions. These results were then applied to the specific model that was used in [37]. Numerical simulations of the model were presented in the end to further show the efficiency of our results [30]. The results developed in this chapter can potentially aide in understanding cancer stem and differentiated cell interaction in tumor growth, thus having the potential to help in designing experiments to develop novel therapeutic strategies against cancer.

CHAPTER 3

MOMENT STABILITY FOR NONLINEAR STOCHASTIC GROWTH KINETICS OF BREAST CANCER STEM CELLS WITH TIME-DELAYS¹

3.1 INTRODUCTION

Breast cancer is a malignant disease with a heterogeneous distribution of cell types. Despite aggressive clinical treatment including surgical resection, radiation, and chemotherapy, tumor recurrence is essentially universal. Therapeutic failure is due, in part, to tumor cell heterogeneity, derived from both genetic and non-genetic sources, which contributes to therapeutic resistance and tumor progression. Understanding this heterogeneity is the key for the development of targeted cancer-preventative and -therapeutic interventions. One of the currently prevailing models explaining intratumoral heterogeneity is the CSC hypothesis [43, 44].

Cancer stem cells (CSCs) are defined as “a small subset of cancer cells” within a cancer that can self-renew and replenish the heterogeneous lineage of cancer cells that comprise the tumor. CSCs are often resistant to chemotherapeutic drugs, sharing similar gene expression profiles and properties with normal stem cells such as formation of spheres in culture, and may be responsible for tumor relapse and metastasis [45–47]. A broad range of CSC frequency, often spanning multiple orders of magnitude, has been observed in human solid tumors of various organ types [48–52]. According

¹42.

to the CSC hypothesis [45], CSCs possess the ability to divide either symmetrically to yield two identical immortal cancer stem cells; or asymmetrically, to simultaneously self-renew and yield one mortal non-stem cancer cell with finite replicative potential [49]. The proportion of CSCs has been speculated to be maintained through alternative use of symmetric and asymmetric division. However, it is largely unknown how to control the switch between these two dividing modes. Mathematical modeling has been utilized to study underlying mechanistic principles and to help design appropriate experiments for better understanding of complex dynamics and interactions of tumor cell populations [53].

In [40], via the contraction fixed point theorem, the exponential stability has been achieved in mean square of the stochastic neutral cellular neural network. Motivated by [40], this chapter will investigate the moment stability of nonlinear stochastic systems of breast cancer stem cells with time-delays based on comparison principle, variation-of-constants formula and linear matrix inequality (LMI) techniques [42].

The rest of the chapter is organized in the following. In Section 3.2, we will generalize the population dynamics with different cell types by a system of differential equations, and introduce some notations. In Section 3.3, we will study the stability properties in mean square of the stochastic system as developed in Section 3.2. In Section 3.4, some numerical examples are provided to further demonstrate the results. Finally, a brief conclusion is drawn.

3.2 PRELIMINARIES

In [37], a mathematical model has been developed to explore the growth kinetics of CSC population both in vitro and in vivo. Here we denote $x_i(t)$ the number of cells at time t for cell types $i, i = 0, 1, \dots, n-1$. P_i the probability that the cell type i is divided into a pair of itself, Q_i the probability that the cell type i is divided into a pair of next cell lineage (cell type $i+1$). Thus $1 - P_i - Q_i$ denotes the probability

that an asymmetric cell division takes place from cell type i to cell type $i - 1$. Here v_i is the synthesis rate which quantifies the speed for cell type i to divide in unit time, d_i is the degradation rate, and $w(t) = (w_1(t), w_2(t), \dots, w_m(t))^T \in R^m$ is a m -dimensional Brownian motion defined on a complete probability space (Ω, \mathcal{F}, P) . The stochastic disturbance term, $h_j^{k,i}(t, u_1, u_2) \in C(R \times R^+ \times R^+)(k, i = 0, 1, \dots, n-1, j = 1, 2, \dots, m)$, can be viewed as stochastic perturbations on the stem cells states and delayed stem cells states. Here τ is a positive constant, $P_i > 0$, $Q_i > 0$, $\nu_i > 0$ ($i = 0, 1, 2, \dots, n-2$) are all decreasing functions of x_{n-1} , which represents the negative feedback from the terminally differentiated cell type $n-1$. Based on the model as developed in [37], a general population dynamics of different cell types can be described by a system of stochastic ordinary differential equations,

$$\begin{aligned}
dx_0(t) &= \{[P_0(x_{n-1}(t-\tau)) - Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t) \\
&\quad - d_0x_0(t)\}dt + \sum_{j=1}^m \sum_{i=0}^{n-1} [h_j^{0,i}(t, x_i(t), x_i(t-\tau))]dw_j(t), \\
dx_1(t) &= \{[1 - P_0(x_{n-1}(t-\tau)) + Q_0(x_{n-1}(t-\tau))]\nu_0(x_{n-1}(t-\tau))x_0(t) \\
&\quad + [P_1(x_{n-1}(t-\tau)) - Q_1(x_{n-1}(t-\tau))]\nu_1(x_{n-1}(t-\tau))x_1(t) - d_1x_1(t)\}dt \\
&\quad + \sum_{j=1}^m \sum_{i=0}^{n-1} [h_j^{1,i}(t, x_i(t), x_i(t-\tau))]dw_j(t), \\
&\vdots \\
dx_{n-2}(t) &= \{[1 - P_{n-3}(x_{n-1}(t-\tau)) + Q_{n-3}(x_{n-1}(t-\tau))] \\
&\quad \times \nu_{n-3}(x_{n-1}(t-\tau))x_{n-3}(t) \\
&\quad + [P_{n-2}(x_{n-1}(t-\tau)) - Q_{n-2}(x_{n-1}(t-\tau))]\nu_{n-2}(x_{n-1}(t-\tau))x_{n-2}(t) \\
&\quad - d_{n-2}x_{n-2}(t)\}dt + \sum_{j=1}^m \sum_{i=0}^{n-1} [h_j^{n-2,i}(t, x_i(t), x_i(t-\tau))]dw_j(t),
\end{aligned}$$

$$\begin{aligned}
dx_{n-1}(t) = & \{[1 - P_{n-2}(x_{n-1}(t - \tau)) + Q_{n-2}(x_{n-1}(t - \tau))] \\
& \times \nu_{n-2}(x_{n-1}(t - \tau))x_{n-2}(t) \\
& - d_{n-1}x_{n-1}(t)\}dt + \sum_{j=1}^m [\sum_{i=0}^{n-1} h_j^{n-1,i}(t, x_i(t), x_i(t - \tau))]dw_j(t)
\end{aligned} \tag{1.1}$$

Let (Ω, \mathcal{F}, P) be a complete probability space with a filtration $\{\mathcal{F}_t\}_{t \geq 0}$ satisfying the usual conditions, i.e. it is right continuous and \mathcal{F}_0 contains all P -null sets. Let $C_{\mathcal{F}_0}^b([-\tau, 0]; R)$ be the family of all bounded, \mathcal{F}_0 -measurable functions. We denote by $C([-\tau, 0]; R)$ the family of all continuous functions $\phi : [-\tau, 0] \rightarrow R$ with

$$\|\phi\|_2 = \sup_{-\tau \leq \theta \leq 0} |\phi(\theta)|_1.$$

Since P_i , Q_i and ν_i ($i = 0, 1, 2, \dots, n-2$) are all decreasing functions of x_{n-1} , there exist some positive constants \bar{P}_i , \bar{Q}_i and $\bar{\nu}_i$ such that

$$P_i(x_{n-1}) \leq \bar{P}_i, \quad Q_i(x_{n-1}) \leq \bar{Q}_i, \quad \nu_i(x_{n-1}) \leq \bar{\nu}_i \quad \text{for } (i = 0, \dots, n-2). \tag{1.2}$$

To simplify, we can rewrite (1.1) as

$$dx = [F(t, x(t), x(t - \tau)) - Dx(t)]dt + \sum_{j=1}^m H_j(t, x(t), x(t - \tau))dw_j(t) \tag{1.3}$$

with the initial condition

$$x(s) = \varphi(s) \in C([-\tau, 0]; R^n), \quad -\tau \leq s \leq 0, \tag{1.4}$$

where $x(t) = (x_0(t), x_1(t), \dots, x_{n-1}(t))^T$, $D = \text{diag}(d_0, d_1, \dots, d_{n-1})$,

$$H_j(t, x(t), x(t - \tau)) = \begin{pmatrix} \sum_{i=0}^{n-1} h_j^{0,i}(t, x_i(t), x_i(t - \tau)) \\ \sum_{i=0}^{n-1} h_j^{1,i}(t, x_i(t), x_i(t - \tau)) \\ \vdots \\ \sum_{i=0}^{n-1} h_j^{n-2,i}(t, x_i(t), x_i(t - \tau)) \\ \sum_{i=0}^{n-1} h_j^{n-1,i}(t, x_i(t), x_i(t - \tau)) \end{pmatrix},$$

$$\begin{aligned}
F(t, x(t), x(t - \tau)) &= \begin{pmatrix} f_1 \\ f_2 \\ \vdots \\ f_{n-2} \\ f_{n-1} \end{pmatrix} = A(x_{n-1}(t - \tau)) \begin{pmatrix} x_0 \\ x_1 \\ \vdots \\ x_{n-2} \\ x_{n-1} \end{pmatrix} \\
&= \begin{pmatrix} [P_0(x_{n-1}(t - \tau)) - Q_0(x_{n-1}(t - \tau))] \\ \quad \times \nu_0(x_{n-1}(t - \tau))x_0(t) \\ \\ [1 - P_0(x_{n-1}(t - \tau)) + Q_0(x_{n-1}(t - \tau))] \\ \quad \times \nu_0(x_{n-1}(t - \tau))x_0(t) \\ + [P_1(x_{n-1}(t - \tau)) - Q_1(x_{n-1}(t - \tau))] \\ \quad \times \nu_1(x_{n-1}(t - \tau))x_1(t) \\ \\ \vdots \\ \\ [1 - P_{n-3}(x_{n-1}(t - \tau)) + Q_{n-3}(x_{n-1}(t - \tau))] \\ \quad \times \nu_{n-3}(x_{n-1}(t - \tau))x_{n-3}(t) \\ + [P_{n-2}(x_{n-1}(t - \tau)) - Q_{n-2}(x_{n-1}(t - \tau))] \\ \quad \times \nu_{n-2}(x_{n-1}(t - \tau))x_{n-2}(t) \\ \\ [1 - P_{n-2}(x_{n-1}(t - \tau)) + Q_{n-2}(x_{n-1}(t - \tau))] \\ \quad \times \nu_{n-2}(x_{n-1}(t - \tau))x_{n-2}(t) \end{pmatrix},
\end{aligned}$$

$$A(x_{n-1}(t - \tau)) =$$

$$= \begin{pmatrix} [P_0 - Q_0]\nu_0 & 0 & \cdots & \\ [1 - P_0 + Q_0]\nu_0 & [P_1 - Q_1]\nu_1 & \cdots & \\ \vdots & \vdots & \vdots & \\ 0 & 0 & \cdots & \\ 0 & 0 & \cdots & \\ \cdots & 0 & & 0 & 0 \\ \cdots & 0 & & 0 & 0 \\ \vdots & \vdots & & \vdots & \vdots \\ \cdots & [1 - P_{n-3} + Q_{n-3}]\nu_{n-3} & & [P_{n-2} - Q_{n-2}]\nu_{n-2} & 0 \\ \cdots & 0 & & [1 - P_{n-2} + Q_{n-2}]\nu_{n-2} & 0 \end{pmatrix}.$$

Let $B = [b_{ij}(t)]_{n \times n}$ with

$$|x(t)|_1 = \sum_{i=1}^n |x_i(t)|,$$

and

$$\|B(t)\|_3 = \sum_{i,j=1}^n |b_{ij}(t)|.$$

We denote the mathematical expectation by E throughout the paper.

Definition 2.1. The system (1.3) with the initial condition is said to be the first moment exponentially stable if there exist two positive constants μ and β such that

$$\|Ex(t; \varphi)\|_2 \leq \mu \|\varphi\|_2 e^{-\beta t}, \quad t \geq 0. \quad (2.1)$$

Definition 2.2. The system (1.3) with the initial condition is said to be exponentially stable in mean square if there exists a solution x of (1.3) and there exists a pair of positive constants μ and β with

$$E\|x(t; \varphi)\|_2^2 \leq \mu E\|\varphi\|_2^2 e^{-\beta t}, \quad t \geq 0. \quad (2.2)$$

Definition 2.3. The system (1.3) with the initial condition is said to be globally exponentially stable in mean square if there exists a scalar $\varsigma > 0$, such that

$$\limsup_{t \rightarrow \infty} \frac{1}{t} \log(E\|x(t; \varphi)\|_2^2) \leq -\varsigma. \quad (2.3)$$

Let $C^{1,2}(R^+ \times R^n; R^+)$ denote the family of all nonnegative functions $V(t, x)$ on $R^+ \times R^n$ which are continuously twice differentiable in x and once differentiable in t . In order to study the mean square globally exponential stability, for each $V \in C^{1,2}([-\tau, \infty) \times R^+; R^+)$, define an operator LV , associated with the uncertain stochastic neural networks with multiple mixed time-delays (1.3), from $(R^+ \times C[-\tau^*, \infty); R^n)$ to R by

$$\begin{aligned} LV(t, x) = & \frac{1}{2} \text{trace} \left[\left(\sum_{j=1}^m H_j^T(t, x(t), x(t-\tau)) \right) V_{xx}(t, x) \right. \\ & \times \left. \left(\sum_{j=1}^m H_j(t, x(t), x(t-\tau)) \right) \right] \\ & + V_t(t, x) + V_x(t, x) [F(t, x(t), x(t-\tau)) - Dx(t)], \end{aligned}$$

where

$$\begin{aligned} V_t(t, x) &= \left(\frac{\partial V(t, x)}{\partial t} \right), \\ V_x(t, x) &= \left(\frac{\partial V(t, x)}{\partial x_1}, \frac{\partial V(t, x)}{\partial x_2}, \dots, \frac{\partial V(t, x)}{\partial x_n} \right), \\ V_{xx}(t, x) &= \left(\frac{\partial^2 V(t, x)}{\partial x_i \partial x_j} \right)_{n \times n}. \end{aligned}$$

3.3 STABILITY OF NONLINEAR STOCHASTIC SYSTEMS OF BREAST CANCER STEM CELLS WITH TIME-DELAYS

In this section, we will study the stability properties in mean square of the stochastic nonlinear growth kinetics of breast cancer stem cells.

Throughout this paper, we always assume the following:

(A₁) there exist positive constants $\alpha^{(j)}$, and positive definite constant matrices $C_j^{(0)}$, $\tilde{C}_j^{(0)}$, $C_j^{(1)}$, $\tilde{C}_j^{(1)}$, $C_j^{(2)}$ and $\tilde{C}_j^{(2)}$ such that

$$\begin{aligned} & \|H_j(t, x(t), x(t-\tau(t))) - H_j(t, y(t), y(t-\tau(t)))\|_2 \\ & \leq \alpha^{(j)} [\|x - y\|_1 + \|x(t-\tau(t)) - y(t-\tau(t))\|_2] \end{aligned}$$

and

$$\begin{aligned}
& \|\tilde{C}_j^{(0)}\|_3 + x^T(t)\tilde{C}_j^{(1)}x(t) + x^T(t-\tau)\tilde{C}_j^{(2)}x(t-\tau) \\
& \leq H_j^T(t, x(t), x(t-\tau)) \times H_j(t, x(t), x(t-\tau)) \\
& \leq \|C_j^{(0)}\|_3 + x^T(t)C_j^{(1)}x(t) + x^T(t-\tau)C_j^{(2)}x(t-\tau),
\end{aligned}$$

where T represents the transpose, $j = 1, 2, \dots, \dots, m$, and

$$H_j(t, x(t), x(t-\tau)) = \begin{pmatrix} \sum_{i=0}^{n-1} h_j^{0,i}(t, x_i(t), x_i(t-\tau)) \\ \sum_{i=0}^{n-1} h_j^{1,i}(t, x_i(t), x_i(t-\tau)) \\ \vdots \\ \sum_{i=0}^{n-1} h_j^{n-2,i}(t, x_i(t), x_i(t-\tau)) \\ \sum_{i=0}^{n-1} h_j^{n-1,i}(t, x_i(t), x_i(t-\tau)) \end{pmatrix}.$$

Note from (1.3) and (1.4) that

$$\begin{aligned}
x(t) &= \exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s-\tau))]ds \\
&+ \sum_{j=1}^m \int_0^t H_j(s, x(s), x(s-\tau)) \exp(Ds)dw(s)\}.
\end{aligned} \tag{3.1}$$

From (A_1) we have that $F(\cdot, \cdot, \cdot)$ and $H_j(\cdot, \cdot, \cdot)$ satisfy the Lipschitzian condition.

Then there is a unique solution of the system (1.1) through (t, φ) .

3.1. The first moment stability.

Let $x(t)$ be the solution of (1.1) and (1.2), we have from (3.1)

$$\|Ex(t; \varphi)\|_2 = \|\exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s-\tau))]ds\|_2. \tag{3.2}$$

Now, we consider the following deterministic equation

$$\begin{cases} dx = [-Dx(t) + F(t, x(t), x(t-\tau))]dt, \\ x(s) = \varphi(s) \in C([- \tau, 0]; R^n), \quad -\tau \leq s \leq 0. \end{cases} \tag{3.3}$$

Let $x_\varphi(t)$ be the solution of (3.3).

Theorem 3.1. *Suppose*

(A₂) *The solution of (3.3) is exponentially stable, i.e., there exist two positive constants κ and λ such that*

$$\|x_\varphi(t)\|_2 \leq \kappa \|\varphi\|_2 e^{-\lambda t}, \quad t \geq 0.$$

Then the system (1.1) is first moment exponentially stable, i.e.,

$$\|Ex(t; \varphi)\|_2 = \|x_\varphi(t)\|_2 \leq \kappa \|\varphi\|_2 e^{-\lambda t}, \quad t \geq 0. \quad (3.4)$$

Proof of Theorem 3.1. The result follows from (A₂) and (3.2). □

Remark 1. In fact, if the equilibrium of the system (3.3) is stable, or asymptotically stable, then the equilibrium of the system (1.1) is also stable in first moment, or asymptotically stable in first moment, respectively, i.e., the stability of the system (3.3) implies the same stability of the system (1.1) in first moment.

For convenience, in the following discussions, we always assume that the system (1.1) is first moment exponentially stable.

3.2. Mean square stability.

Now we study the stability in mean square of the system (1.1).

Since $dw_j ds = 0$, $E dw_j = 0$ and $E(dw_j(s), dw_k(s)) = \delta_{jk} ds$ ($j, k = 1, 2, \dots, m$), we have from the definitions of $\|\cdot\|_1$, $\|\cdot\|_2$, $\|\cdot\|_3$ and (3.1) that

$$\begin{aligned} E|x(t)|_1^2 &= E|\exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s-\tau))]ds \\ &\quad + \sum_{j=1}^m \int_0^t H_j(s, x(s), x(s-\tau)) \exp(Ds) dw(s)\}|_1^2 \\ &\leq E\{2\|\varphi(0)\|_2^2 \|\exp(-Dt)\|_3^2 + 2 \int_0^t \|\exp D(s-t)F(s, x(s), x(s-\tau))\|_2^2 ds \\ &\quad + \int_0^t \|\exp D(s-t)\|_3^2 [\sum_{j=1}^m H_j^T(s, x(s), x(s-\tau))\end{aligned}$$

$$\begin{aligned}
& \times H_j(s, x(s), x(s - \tau))]ds\} \\
& \leq E\{2n^2\|\varphi(0)\|_2^2 e^{-2\lambda_{\min}(D)t} + 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \|A(x_{n-1}(s - \tau))\|_3^2 \\
& \times |x(s)|_1^2 ds + \int_0^t n^2 e^{2\lambda_{\min}(D)(s-t)} [\sum_{j=1}^m (\|C_j^{(0)}\|_3 + x^T(s)C_j^{(1)}x(s) \\
& + x^T(s - \tau)C_j^{(2)}x(s - \tau))]ds\} \\
& \leq E\{2n^2\|\varphi(0)\|_2^2 e^{-2\lambda_{\min}(D)t} + 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
& \times [\sum_{i=0}^{n-2} \bar{\nu}_i(1 + 2\bar{P}_i + 2\bar{Q}_i)]^2 |x(s)|_1^2 ds + \int_0^t n^2 e^{2\lambda_{\min}(D)(s-t)} \\
& \times [\sum_{j=1}^m (\|C_j^{(0)}\|_3 + x^T(s)C_j^{(1)}x(s) + x^T(s - \tau)C_j^{(2)}x(s - \tau))]ds\} \\
& \leq E\{\Phi e^{-2\lambda_{\min}(D)t} + \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
& \times [\bar{C}^{(0)} + \bar{C}^{(1)}|x(s)|_1^2 + \bar{C}^{(2)}\|x(s - \tau)\|_2^2]ds\} \\
& = \Phi e^{-2\lambda_{\min}(D)t} + E \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\
& \times [\bar{C}^{(0)} + \bar{C}^{(1)}|x(s)|_1^2 + \bar{C}^{(2)}\|x(s - \tau)\|_2^2]ds, \tag{3.5}
\end{aligned}$$

where $\lambda_{\min}(D)$ represents the minimal eigenvalue of matrix D , $\lambda_{\max}(C_j^{(0)})$, $\lambda_{\max}(C_j^{(1)})$ and $\lambda_{\max}(C_j^{(2)})$ represent the maximal eigenvalues of $C_j^{(0)}$, $C_j^{(1)}$ and $C_j^{(2)}$ ($j = 1, 2, \dots, m$),

$$\Phi = 2n^2\|\varphi(0)\|_2^2, \quad \bar{C}^{(0)} = n^3 \sum_{j=1}^m \lambda_{\max}(C_j^{(0)}), \quad \bar{C}^{(2)} = n^3 \sum_{j=1}^m \lambda_{\max}(C_j^{(2)})$$

$$\bar{C}^{(1)} = n^3 \sum_{j=1}^m \lambda_{\max}(C_j^{(1)}) + 2n^2 [\sum_{i=0}^{n-2} \bar{\nu}_i(1 + 2\bar{P}_i + 2\bar{Q}_i)]^2,$$

$$\exp D(s-t) = \begin{pmatrix} e^{d_0(s-t)} & 0 & 0 & \dots & 0 \\ 0 & e^{d_1(s-t)} & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & e^{d_{n-1}(s-t)} \end{pmatrix}$$

and

$$\|\exp D(s-t)\|_3 = \sum_{i=0}^{n-1} e^{d_i(s-t)}.$$

Theorem 3.2. *Let (A_1) and (A_2) be satisfied. Then*

$$E|x(t)|_1^2 \leq u(t), \quad t \geq 0,$$

where $u(t)$ is the solution of the comparison equation

$$\begin{cases} \dot{u}(t) = (-2\lambda_{\min}(D) + \overline{C}^{(1)})u(t) + \overline{C}^{(2)}u(t-\tau) + \overline{C}^{(0)}, & t \geq 0, \\ u(s) \geq \Phi \geq 0, & s \in [-\tau, 0]. \end{cases} \quad (3.6)$$

Proof of Theorem 3.2. Let

$$\begin{cases} M(t) = \Phi e^{-2\lambda_{\min}(D)t} \\ + E \int_0^t e^{2\lambda_{\min}(D)(s-t)} [\overline{C}^{(0)} + \overline{C}^{(1)}|x(s)|_1^2 + \overline{C}^{(2)}\|x(s-\tau)\|_2^2] ds, \\ M(s) \geq \Phi, \quad s \in [-\tau, 0]. \end{cases} \quad (3.7)$$

We have from (3.5) and (3.7)

$$\begin{aligned} \dot{M}(t) &= -2\lambda_{\min}(D)\{\Phi e^{-2\lambda_{\min}(D)t} + E \int_0^t e^{2\lambda_{\min}(D)(s-t)} [\overline{C}^{(0)} + \overline{C}^{(1)}|x(s)|_1^2 \\ &\quad + \overline{C}^{(2)}\|x(s-\tau)\|_2^2] ds\} + \overline{C}^{(0)} + \overline{C}^{(1)}E|x(t)|_1^2 + \overline{C}^{(2)}E\|x(t-\tau)\|_2^2 \\ &\leq -2\lambda_{\min}(D)M(t) + \overline{C}^{(0)} + \overline{C}^{(1)}M(t) + \overline{C}^{(2)}M(t-\tau) \\ &= (-2\lambda_{\min}(D) + \overline{C}^{(1)})M(t) + \overline{C}^{(2)}M(t-\tau) + \overline{C}^{(0)}, \quad t \geq 0. \end{aligned}$$

From (3.7), let $u(s) = M(s)$, $s \in [-\tau, 0]$. From the comparison theorem of ordinary differential equations, we get $u(t) \geq M(t)$, $t \geq 0$, $u(s) \geq M(s)$, $s \in [-\tau, 0]$, and thus

$$E|x(t)|_1^2 \leq M(t) \leq u(t), \quad t \geq 0.$$

The proof is complete. \square

Theorem 3.3. *If the assumptions of Theorem 3.2 are satisfied, and the equilibrium of system (3.6) is stable, or asymptotically stable, then the equilibrium of system (1.1) is also stable in mean square, or asymptotically stable in mean square, respectively, i.e., the stability of system (3.6) implies the same stability of system (1.1) in mean square.*

3.3. Mean square instability.

Similar reasoning as in (3.5), we have from the definition of $|\cdot|_1$ and (3.1) that

$$\begin{aligned} E|x(t)|_1^2 &= E|\exp(-Dt)\{\varphi(0) + \int_0^t \exp(Ds)[F(s, x(s), x(s-\tau))]ds \\ &\quad + \sum_{j=1}^m \int_0^t H_j(s, x(s), x(s-\tau(s))) \exp(Ds)dw(s)\}|_1^2 \\ &= E\{\|\exp(-Dt)\|_3^2[\varphi(0) + \int_0^t \exp(Ds)F(s, x(s), x(s-\tau))ds]^T \\ &\quad \times [\varphi(0) + \int_0^t \exp(Ds)F(s, x(s), x(s-\tau))ds] \\ &\quad + \int_0^t \|\exp D(s-t)\|_3^2[\sum_{j=1}^m H_j^T(s, x(s), x(s-\tau)) \\ &\quad \times H_j(s, x(s), x(s-\tau))]ds\} \\ &\geq E\{\int_0^t n^2 e^{2\lambda_{\max}(D)(s-t)}[\sum_{j=1}^m (n\lambda_{\min}(\tilde{C}_j^{(0)}) + n\lambda_{\min}(\tilde{C}_j^{(1)})|x(s)|_1^2 \\ &\quad + n\lambda_{\min}(\tilde{D}_j^{(2)})|x(s-\tau)|_1^2)]ds - 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \\ &\quad \times \|A(x_{n-1}(s-\tau))\|_3^2|x(s)|_1^2 ds\} \end{aligned}$$

$$\begin{aligned}
&\geq E\left\{\int_0^t n^3 e^{2\lambda_{\max}(D)(s-t)} \left[\sum_{j=1}^m (\lambda_{\min}(\tilde{C}_j^{(1)})|x(s)|_1^2 \right. \right. \\
&\quad \left. \left. + \lambda_{\min}(\tilde{D}_j^{(2)})|x(s-\tau)|_1^2 + \lambda_{\min}(\tilde{C}_j^{(0)})\right] ds \right. \\
&\quad \left. - 2n^2 \int_0^t e^{2\lambda_{\min}(D)(s-t)} \left[\sum_{i=0}^{n-2} \bar{\nu}_i(1+2\bar{P}_i+2\bar{Q}_i)\right]^2 |x(s)|_1^2 ds \right\} \\
&= E \int_0^t e^{2\lambda_{\max}(D)(s-t)} [\hat{C}^{(0)} + \hat{C}^{(1)}|x(s)|_1^2 + \hat{C}^{(2)}\|x(s-\tau)\|_2^2] ds, \quad (3.8)
\end{aligned}$$

where $\lambda_{\max}(D)$ represents the maximal eigenvalue of D , $\lambda_{\min}(\tilde{C}_j^{(1)})$ and $\lambda_{\min}(\tilde{C}_j^{(2)})$ represent the minimal eigenvalues of $\tilde{C}_j^{(1)}$ and $\tilde{C}_j^{(2)}$ ($j = 1, 2, \dots, m$),

$$\begin{aligned}
\hat{C}^{(0)} &= n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(0)}), \quad \hat{C}^{(2)} = n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(2)}), \\
\hat{C}^{(1)} &= n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(1)}) - 2n^2 [\sum_{i=0}^{n-2} \bar{\nu}_i(1+2\bar{P}_i+2\bar{Q}_i)]^2.
\end{aligned}$$

Theorem 3.4. *Suppose*

- 1) *The assumptions (A_1) and (A_2) are satisfied;*
- 2)

$$\hat{C}^{(1)} = n^3 \sum_{j=1}^m \lambda_{\min}(\tilde{C}_j^{(1)}) - 2n^2 [\sum_{i=0}^{n-2} \bar{\nu}_i(1+2\bar{P}_i+2\bar{Q}_i)]^2 > 0.$$

Then

$$E|x(t)|_1^2 \geq u(t), \quad t \geq 0,$$

where $u(t)$ is the solution of the comparison equation

$$\begin{cases} \dot{u}(t) = (-2\lambda_{\max}(D) + \hat{C}^{(1)})u(t) + \hat{C}^{(2)}u(t-\tau) + \hat{C}^{(0)}, & t \geq 0, \\ u(s) \geq 0, & s \in [-\tau, 0]. \end{cases} \quad (3.9)$$

Proof of Theorem 3.4. Let

$$\begin{cases} M(t) = E \int_0^t e^{2\lambda_{\max}(D)(s-t)} [\hat{C}^{(0)} + \hat{C}^{(1)}|x(s)|_1^2 + \hat{C}^{(2)}\|x(s-\tau)\|_2^2] ds, \\ M(s) \geq 0, & s \in [-\tau, 0]. \end{cases} \quad (3.10)$$

We have from (3.10)

$$\begin{aligned}
\dot{M}(t) &= -2\lambda_{\max}(D)E \int_0^t e^{2\lambda_{\max}(D)(s-t)} [\hat{C}^{(0)} + \hat{C}^{(1)}|x(s)|_1^2 + \hat{C}^{(2)}\|x(s-\tau)\|_2^2] ds \\
&\quad + \hat{C}^{(0)} + \hat{C}^{(1)}E|x(t)|_1^2 + \hat{C}^{(2)}E\|x(t-\tau)\|_2^2 \\
&\geq -2\lambda_{\max}(D)M(t) + \hat{C}^{(0)} + \hat{C}^{(1)}M(t) + \hat{C}^{(2)}M(t-\tau) \\
&= (-2\lambda_{\max}(D) + \hat{C}^{(1)})M(t) + \hat{C}^{(2)}M(t-\tau) + \hat{C}^{(0)}.
\end{aligned}$$

From (3.10), let $u(s) = M(s)$, $s \in [-\tau, 0]$. By the comparison theorem of ordinary differential equations, we get $u(t) \leq M(t)$, $t \geq 0$, and thus

$$E|x(t)|_1^2 \geq M(t) \geq u(t), \quad t \geq 0.$$

The proof is complete. □

Theorem 3.5. *If the assumptions of Theorem 3.4 are satisfied, and the equilibrium of system (3.10) is unbounded, then the equilibrium of system (1.1) is also unbounded in mean square, i.e., the unboundedness of system (3.10) implies the same unboundedness of system (1.1) in mean square.*

3.4. Mean square globally exponentially stable.

Theorem 3.6. *Suppose (A_1) and (A_2) hold and assume that there exist matrices $P > 0$, $Q > 0$, $M_0 \geq 0$ and $M_i \geq 0$ ($j = 1, 2, \dots, m$) such that*

$$\begin{aligned}
&\text{trace}[\sum_{j=1}^m H_j^T(t, x(t), x(t-\tau))PH_j(t, x(t), x(t-\tau))] \\
&\leq x^T(t)M_0x(t) + \sum_{j=1}^m x^T(t-\tau)M_jx(t-\tau).
\end{aligned} \tag{3.11}$$

Then system (1.1) is globally exponentially stable in mean square, if there exist positive scalars $\mu > 0$, $\rho > 0$ and positive definite matrices $\Gamma_i > 0$ ($i = 1, 2, \dots, m$) such that

the LMI holds:

$$\begin{pmatrix} -PD - DP + \mu Q + M_0 & 0 \\ + \sum_{j=1}^m \rho \Gamma_j + 2 \sum_{i=1}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i) P & \\ 0 & \sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q \end{pmatrix} < 0.$$

Proof of Theorem 3.6. Let

$$V(t, x(t)) = x^T(t) P x(t) + \mu \int_{t-\tau}^t x^T(s) Q x(s) ds + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s) \Gamma_j x(s) ds. \quad (3.12)$$

From Itô's differential formula (see, e.g., [12]) we have along (1.3)

$$\begin{aligned} LV(t, x(t)) &= x^T(t) [-PD - DP] x(t) \\ &+ \text{trace} \sum_{j=1}^m H_j^T(t, x(t), x(t-\tau)) P H_j(t, x(t), x(t-\tau)) \\ &+ 2x^T(t) P F(t, x(t), x(t-\tau)) + \mu x^T(t) Q x(t) + \sum_{j=1}^m \rho x^T(t) \Gamma_j x(t) \\ &- \mu x^T(t-\tau) Q x(t-\tau) - \sum_{j=1}^m \rho x^T(t-\tau) \Gamma_j x(t-\tau). \end{aligned} \quad (3.13)$$

From (3.11) and (3.13), we have that

$$\begin{aligned} LV(t, x(t)) &\leq x^T(t) [-PD - DP + \mu Q + M_0 + \sum_{j=1}^m \rho \Gamma_j] x(t) \\ &+ 2x^T(t) P A(x_{n-1}(t-\tau)) x(t) \\ &+ x^T(t-\tau) [\sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q] x(t-\tau) \\ &\leq x^T(t) [-PD - DP + \mu Q + M_0 + \sum_{j=1}^m \rho \Gamma_j] x(t) \\ &+ 2 \sum_{i=1}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i) P x(t) \\ &+ x^T(t-\tau) [\sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q] x(t-\tau) \end{aligned}$$

$$= \xi \Pi \xi^T, \quad (3.14)$$

where

$$\xi = (x^T(t), x^T(t - \tau))$$

and

$$\Pi = \begin{pmatrix} -PD - DP + \mu Q + M_0 + & 0 \\ \sum_{j=1}^m \rho \Gamma_j + 2 \sum_{i=1}^{n-2} \bar{\nu}_i (1 + 2\bar{P}_i + 2\bar{Q}_i) P & \\ 0 & \sum_{j=1}^m (M_j - \rho \Gamma_j) - \mu Q \end{pmatrix}.$$

Let $\tilde{V}(t, x(t)) = e^{kt} V(t, x(t))$, where k is to be determined. It is easy to check that

$$V(t, x(t)) \leq \lambda_{\max}(P) |x(t)|_1^2 + \mu \int_{t-\tau}^t x^T(s) Q x(s) ds + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s) \Gamma_j x(s) ds.$$

Thus

$$\begin{aligned} L\tilde{V}(t, x(t)) &= e^{kt} [kV(t, x(t)) + LV(t, x(t))] \\ &\leq e^{kt} \{ \xi^T \Pi \xi + k[\lambda_{\max}(P) |x(t)|_1^2 + \mu \int_{t-\tau}^t x^T(s) Q x(s) ds \\ &\quad + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s) \Gamma_j x(s) ds] \}. \end{aligned} \quad (3.15)$$

Choose k sufficiently small so that

$$\begin{aligned} &\xi^T \Pi \xi + k[\lambda_{\max}(P) |x(t)|_1^2 + \mu \int_{t-\tau}^t x^T(s) Q x(s) ds \\ &\quad + \sum_{j=1}^m \rho \int_{t-\tau}^t x^T(s) \Gamma_j x(s) ds] \leq 0. \end{aligned} \quad (3.16)$$

From (3.15) and (3.16), we have

$$L\tilde{V}(t, x(t)) \leq 0,$$

which implies that

$$E\tilde{V}(t, x(t)) \leq E\tilde{V}(0, x(0)). \quad (3.17)$$

Therefore, we have

$$\begin{aligned}
e^{kt}EV(t, x(t)) &\leq EV(0, x(0)) \\
&\leq E\{\lambda_{\max}(P)|x(0)|_1^2 + \mu \int_{-\tau}^0 x^T(s)Qx(s)ds \\
&\quad + \sum_{j=1}^m \rho \int_{-\tau}^0 x^T(s)\Gamma_j x(s)ds\} \\
&\leq [\lambda_{\max}(P) + \mu\tau\lambda_{\max}(Q) + m\tau\rho\lambda_{\max}(\Gamma)] \max_{-\tau \leq s \leq 0} E|x(s)|_1^2, \quad (3.18)
\end{aligned}$$

where $\lambda_{\max}(\Gamma) = \max\{\lambda_{\max}(\Gamma_1), \lambda_{\max}(\Gamma_2), \dots, \lambda_{\max}(\Gamma_m)\}$. Also, it is easy to see that

$$EV(t, x(t)) \geq \lambda_{\min}(P)|x(t)|_1^2. \quad (3.19)$$

From (3.18) and (3.19), it follows that

$$\begin{aligned}
E|x(t)|_1^2 &\leq \lambda_{\min}^{-1}(P)[\lambda_{\max}(P) + \mu\tau\lambda_{\max}(Q) + m\tau\rho\lambda_{\max}(\Gamma)] \\
&\quad \times e^{-kt} \max_{-\tau \leq s \leq 0} E|x(s)|_1^2. \quad (3.20)
\end{aligned}$$

Thus system (1.1) is globally exponentially stable in mean square. \square

Remark 2. Note that [54] is a special case of system (1.1) and note that the Laplace transform technique fails for system (1.1).

Remark 3. System (1.1) can be generalized to the general form

$$\begin{aligned}
dx &= [-(D + \triangle D(t))x(t) + (B + \triangle B(t))F(t, x(t), x(t - \tau_1(t)), \\
&\quad \dots, x(t - \tau_m(t))) + \sum_{p=1}^k (W_p + \triangle W_p(t)) \int_{t-r_p(t)}^t g_p(x(s))ds]dt \\
&\quad + \sum_{j=1}^l H_j(t, x(t), x(t - \sigma_j(t)))dw(t).
\end{aligned}$$

3.4 EXAMPLES

We consider the following special case of (1.1) with three types of cells as in [37]

$$dx_0 = \left\{ \left[\frac{p_0}{1 + \gamma_1^0(x_2(t - \tau))^2} - \frac{q_0}{1 + \gamma_2^0(x_2(t - \tau))^2} \right] \frac{\nu_0}{1 + \beta_0(x_2(t - \tau))^2} x_0(t) \right.$$

$$\begin{aligned}
& -d_0x_0(t)\}dt + h^0(x_0(t-\tau))dw_0(t), \\
dx_1 = & \{[1 - \frac{p_0}{1 + \gamma_1^0(x_2(t-\tau))^2} + \frac{q_0}{1 + \gamma_2^0(x_2(t-\tau))^2}]\frac{\nu_0}{1 + \beta_0(x_2(t-\tau))^2}x_0(t) \\
& + [\frac{p_1}{1 + \gamma_1^1(x_2(t-\tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t-\tau))^2}]\frac{\nu_1}{1 + \beta_1(x_2(t-\tau))^2}x_1(t) \\
& - d_1x_1(t)\}dt + h^1(x_1(t-\tau))dw_1(t), \\
dx_2 = & \{[1 - \frac{p_1}{1 + \gamma_1^1(x_2(t-\tau))^2} + \frac{q_1}{1 + \gamma_2^1(x_2(t-\tau))^2}]\frac{\nu_1}{1 + \beta_1(x_2(t-\tau))^2}x_1(t) \\
& - d_2x_2(t)\}dt + h^2(x_2(t-\tau))dw_2(t). \tag{4.1}
\end{aligned}$$

Here $x_0(t)$, $x_1(t)$, and $x_2(t)$ are the number of cancer stem cells (CSCs), progenitor cells (PCs), and terminally differentiated cells (TDCs), respectively, at time t . The time-delay τ is 0 for Figure (3.1) and 10 time units for Figure (3.2). There is only one stochastic disturbance term, $h^i(x_i(t-\tau))$, $i = 0, 1, 2$, for each cell type, and it is an explicit function of only the cell type that it affects.

The figures show the solution of (4.1) implemented in MATLAB with initial condition $x(0) = (10, 200, 800)^T$. The parameters and stochastic terms used in each figure are listed in Table (3.1). Figures (3.1) and (3.1) have the same parameters and stochastic terms and differ only in the time delay. Due to the presence of a stochastic term, each figure is the average of ten trials. The x -axis is time units, and the y -axis is number of cells in a log-scale. The inset shows a zoomed-in portion of the graph.

In Figure (3.1)a, there is no noise term. The number of cells shoots up to about 10^4 and then levels off. Equilibrium is reached. In Figure (3.1)b, the noise term is

$$H(x(t)) = \begin{pmatrix} 30 \\ 40 \\ 20 \end{pmatrix}.$$

The number of cells shoots up to about 10^4 and then levels off. Equilibrium is reached, but there is small perturbation around the equilibrium position. In Figure (3.1)c, the noise term is

$$H(x(t)) = \begin{pmatrix} \frac{h_1 x_1^2}{1 + g_1 x_1^2} \\ \frac{h_2 x_2^2}{1 + g_2 x_2^2} \\ \frac{h_3 x_3^2}{1 + g_3 x_3^2} \end{pmatrix}.$$

The number of cells shoots up to about 10^4 and then levels off. Equilibrium is reached, but there is small perturbation around the equilibrium position. In Figure (3.1)d, the noise term is

$$H(x(t)) = \begin{pmatrix} \frac{h_1 x_1^2}{1 + g_1 x_1} \\ \frac{h_2 x_2^2}{1 + g_2 x_2} \\ \frac{h_3 x_3^2}{1 + g_3 x_3} \end{pmatrix}.$$

The number of cells shoots up and increases by orders of magnitude more than the previous scenarios. There is large perturbation. Equilibrium is not reached, but the total number of cells is between 10^6 and 10^{12} .

In Figures (3.2)a, b, and c, the number of cells shoots up to about 10^6 and then levels off. This is 100 times greater than in Figure (3.1). Equilibrium is reached, but there are oscillations in the number of PCs and TDCs around the equilibrium position. The noise term has a negligible effect in Figures (3.2)b and c. In Figure (3.2)d, the number of cells shoots up and increases by orders of magnitude more than the previous scenarios. There is small perturbation. Equilibrium is not reached, and the number of cells grows unboundedly.

The parameters were chosen both from biological data from our collaborator's lab [37] and from requiring that equilibrium is reached. From experiments with tumor cells we know that the degradation rate is the greatest for TDCs, then PCs, and then CSCs. We also know that the equilibrium tumor size is roughly 10^6 total cells from our

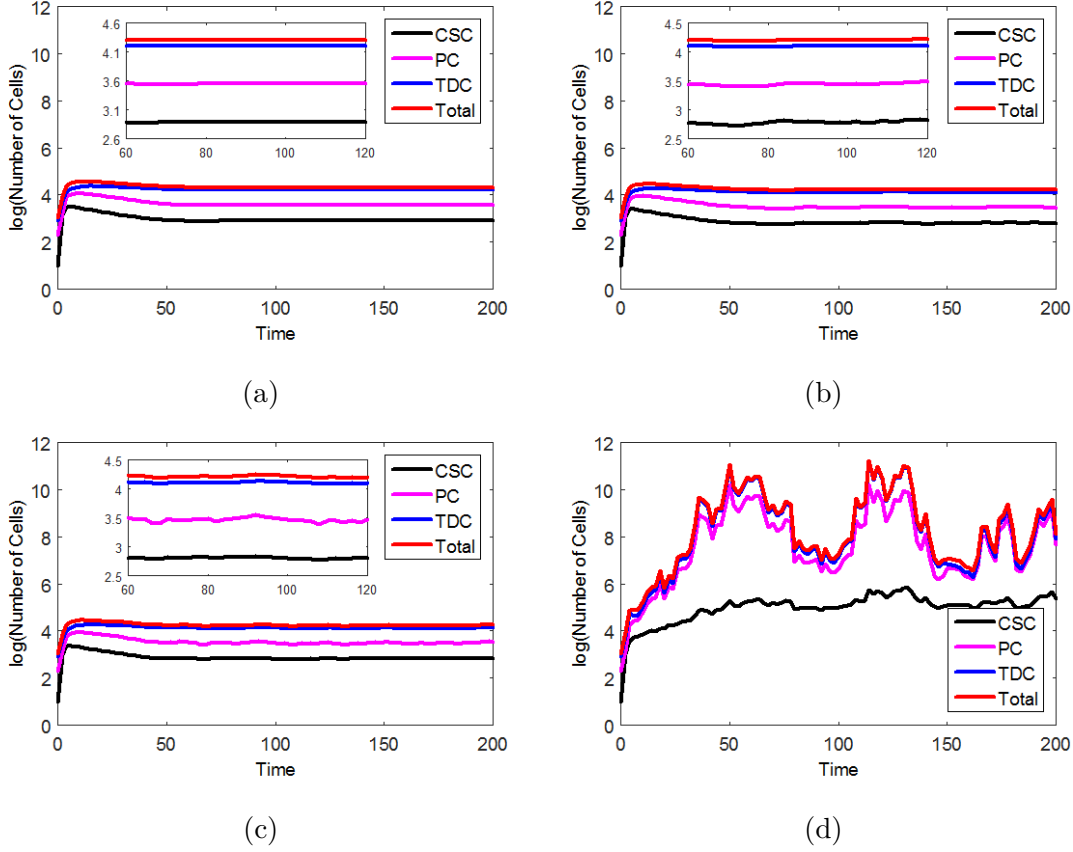


Figure 3.1: Solution of (4.1). Parameters and noise functions are listed in Table (3.1). $\tau = 0$. These are the average of ten trials.

collaborator's lab. Additionally, the probabilities, p_0 , q_0 , p_1 , and q_1 , and degradation rates, d_0 , d_1 , and d_2 , are between 0 and 1 by definition. With these restrictions, the parameters were then chosen through guess and check until equilibrium was reached.

3.5 CONCLUSION

Breast cancer is a malignant disease with a heterogeneous distribution of cell types. Mathematical modeling has been utilized to study underlying mechanistic principles and to help design appropriate experiments for better understanding of complex dynamics and interactions of tumor cell populations. In this chapter, we have studied the moment stability of nonlinear stochastic systems of breast cancer stem cells with time-delays. Based on the technique of the variation-of-constants formula along with

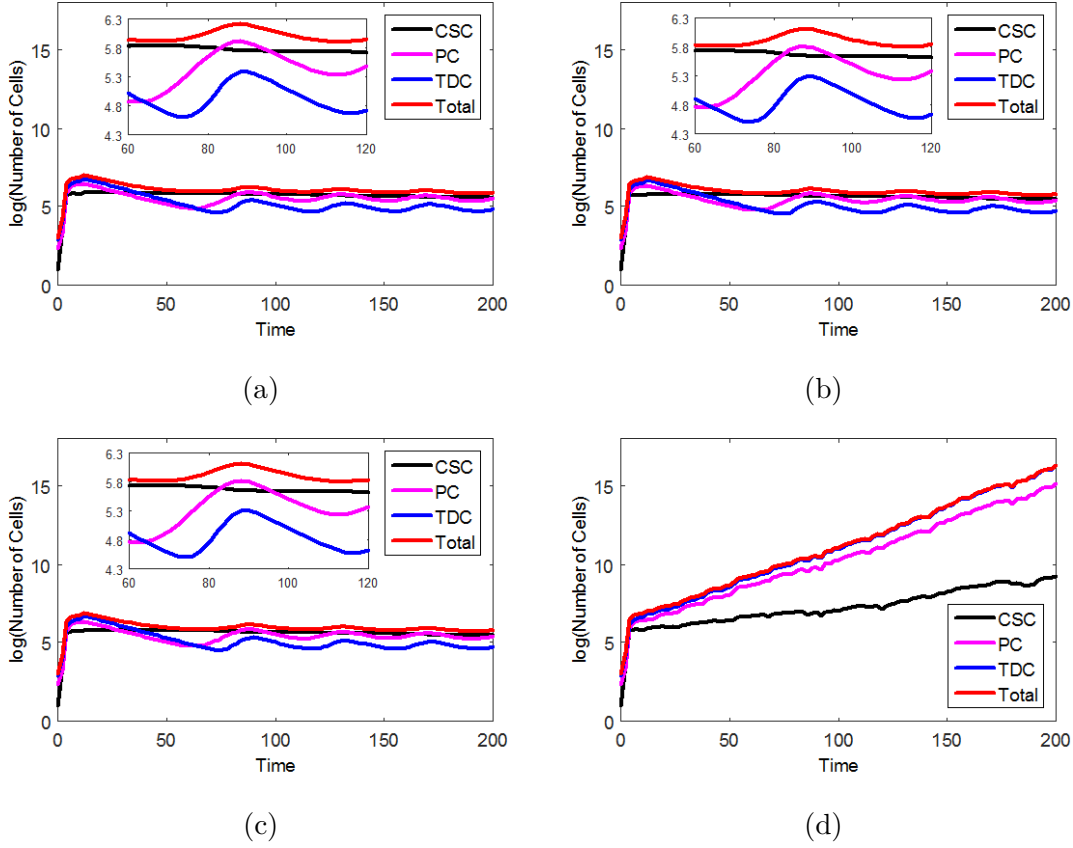


Figure 3.2: Solution of (4.1). Parameters and noise functions are listed in Table (3.1). $\tau = 10$. These are the average of ten trials.

the comparison principle, the moment stability theorems have been established for the systems with the stability properties for the comparative systems. By applying the linear matrix inequality (LMI) technique, we also obtain a criteria for the exponential stability in mean square of the nonlinear stochastic systems. Some numerical examples are performed to further validate the results [42]. As discussed in [37], the results developed in this chapter will help to further reveal the underlying mechanisms to regulate and control the dynamics of cancer tumor growth. Hence the outcome of this study may potentially lead to design novel therapeutic strategies for treating cancer development. We plan next to explore the stochastic dynamics of breast cancer cells with inherent noise perturbation on the variations of different parameters.

Table 3.1: Parameters and noise term used in Figures (3.1) and (3.2).

Parameters or Function	Figure (3.1)a, (3.2)a	Figure (3.1)b, (3.2)b	Figure (3.1)c, (3.2)c	Figure (3.1)d, (3.2)d
p_0	0.5	0.5	0.5	0.5
p_1	0.001	0.001	0.001	0.001
q_0	0.2	0.2	0.2	0.2
q_1	0.9	0.9	0.9	0.9
ν_0	10	10	10	10
ν_1	10	10	10	10
γ_1^0	7×10^{-9}	7×10^{-9}	7×10^{-9}	7×10^{-9}
γ_1^1	2×10^2	2×10^2	2×10^2	2×10^2
γ_2^0	4×10^{-10}	4×10^{-10}	4×10^{-10}	4×10^{-10}
γ_2^1	8×10^{-18}	8×10^{-18}	8×10^{-18}	8×10^{-18}
β_0	3×10^{-8}	3×10^{-8}	3×10^{-8}	3×10^{-8}
β_1	2×10^{-7}	2×10^{-7}	2×10^{-7}	2×10^{-7}
d_0	0.001	0.001	0.001	0.001
d_1	0.08	0.08	0.08	0.08
d_2	0.085	0.085	0.085	0.085
$H(x(t))$	$\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}$	$\begin{pmatrix} 30 \\ 40 \\ 20 \end{pmatrix}$	$\begin{pmatrix} \frac{h_1 x_1^2}{1+g_1 x_1^2} \\ \frac{h_2 x_2^2}{1+g_2 x_2^2} \\ \frac{h_3 x_3^2}{1+g_3 x_3^2} \end{pmatrix}$	$\begin{pmatrix} \frac{h_1 x_1^2}{1+g_1 x_1} \\ \frac{h_2 x_2^2}{1+g_2 x_2} \\ \frac{h_3 x_3^2}{1+g_3 x_3} \end{pmatrix}$
h_0	-	-	300	3
h_1	-	-	5000	10
h_3	-	-	6000	22
g_0	-	-	10	10
g_1	-	-	10	10
g_3	-	-	20	20

CHAPTER 4

MATHEMATICAL MODELING OF HER2 SIGNALING PATHWAY IN BREAST CANCER CELLS

4.1 INTRODUCTION

The cancer stem cell hypothesis states that there is a small subset of tumor cells, called cancer stem cells (CSCs), that are responsible for the proliferation and resistance to therapy of tumors. CSCs have the ability to self-renew and differentiate to form the nontumorigenic cells found in tumors [55]. Studies have shown that over-expression of human epidermal growth factor receptor 2 (HER2) plays a role in regulation of CSC population in breast cancer. As a result, current cancer therapy includes drugs that block HER2 for patients with HER2+ breast cancer. However, patients can develop anti-HER2 drug resistance [56]. Downstream of HER2 is nuclear factor κ B (NF κ B). The aberrant regulation of NF κ B leads to cancer growth through proliferation of CSCs and inhibition of CSC apoptosis. This makes it a promising target for cancer therapy, especially for those who have developed resistance to anti-HER2 treatment [57–59]. Through in vitro experiments, our lab has discovered that interleukin-1 (IL1), which is downstream of HER2, is responsible for NF κ B activation, thus making it a potential target for cancer treatment. We develop a mathematical model of this signaling pathway to better understand its dynamics and to help guide breast cancer treatment.

Several studies have shown that HER2 plays a role in regulation of CSCs in breast cancer. For example, Korkaya, *et al.* show that over-expression of HER2 in

cell populations increases both the CSC population and the tumorigenicity within the population. Current available treatments for HER2+ breast cancer include drugs that inhibit HER2. Although this treatment has been successful for many patients, a fraction of patients develop resistance to these drugs [56]. This has led to the study of the HER2 signaling pathway in order to find alternative targets for cancer therapy. One such protein of interest downstream of HER2 is $\text{NF}\kappa\text{B}$ since aberrant regulation of this protein is found in many types of cancers, including breast cancer, and since it is shown to cause the dangerous features of cancer [59]. Moreover, $\text{NF}\kappa\text{B}$ activation is shown to render HER2+ cells drug resistant. Study of this pathway has shown the following downstream: HER2, AKT, IKK, $\text{NF}\kappa\text{B}$ [57, 58]. This suggests inhibition of $\text{NF}\kappa\text{B}$ alongside anti-HER2 therapy in order to combat anti-HER2 resistance of breast cancer cells. Merkhofer *et al.* propose this to be done by targeting IKK [57]. In vitro experiments in our lab show that HER2 is able to activate $\text{NF}\kappa\text{B}$ through IL1. We propose the following downstream: HER2, ERK, IL1, IKK, $\text{NF}\kappa\text{B}$.

In this chapter, we develop a novel mathematical model of the HER2 signaling pathway. A new feature of the model is the simplified downstream dynamics of the $\text{I}\kappa\text{B}$ - $\text{NF}\kappa\text{B}$ dissociation and association loop. This pathway was first modeled by Hoffmann, *et al.* [60] and has been studied by others since [61–63]. Previous studies have developed complicated models for this interaction by accounting for various reactions and species. Another new feature of the model is the incorporation of IL1 as an intermediary between HER2 and $\text{NF}\kappa\text{B}$, which is a new relationship discovered by our lab. The simplified model fits the experimental data, while the presence of IL1 explains some observed phenomena. We use the model to make predictions for breast cancer treatment scenarios. We also perform global sensitivity analysis on $\text{NF}\kappa\text{B}$ concentration with respect to the parameters to reduce the dimension of the parameter space and identify key reactions in the model [64].

4.2 MODEL

Through studying the literature and running simulations, we propose the following model. HER2 binds to the cell membrane and signals to activate ERK and AKT. ERK activates IL1. AKT and IL1 activate IKK. The pathway from HER2 to IKK through AKT is well known. Our experiments and modeling suggest the new pathway from HER2 to IKK through IL1. IKK phosphorylates the $I\kappa B$ -NF κB complex, causing it to dissociate into p- $I\kappa B$ and p-NF κB . p- $I\kappa B$ then degrades. p-NF κB gives positive feedback to IL1. p-NF κB goes to the nucleus and synthesizes $I\kappa B$. The free nuclear p-NF κB causes cancer growth and is hence the focus of our study. p-NF κB and $I\kappa B$ then associate to form the complex $I\kappa B$ -NF κB [60, 61, 65]. This is schematically represented in Figure 4.1. The HER2 signaling pathway is far more complex than the one shown. However, this model is a simplified representation of the signaling pathway, and it captures the key components needed for our study. There are two novel aspects of this model. One is the incorporation of IL1 in the upstream dynamics. This is important because studying IL1's role in NF κB can provide insight into regulating NF κB for treating patients with HER2+ breast cancer. The other is the simplified dynamics between IKK, $I\kappa B$, and NF κB . A mathematical model of this was proposed in 2002 by Hoffmann, *et al.* which considered the interactions in detail [60]. Since then, others have used this model. We draw upon two simplified versions of this model. Sung, *et al.* considered a time delay for free NF κB 's synthesis of $I\kappa B$ [62]. And Zambrano, *et al.* omitted certain complexes and cytoplasm to nucleus transport [63]. Combining these two approaches with further simplification, we arrive at the model in Figure 4.1. This model simplifies the interaction between IKK, $I\kappa B$, and NF κB , while still capturing the dynamics, as shown by the model's ability to reproduce our experimental data. Moreover, some phenomena are explained by IL1's presence in this pathway and its positive feedback from NF κB .

The equations used to represent the concentrations of each protein are based on

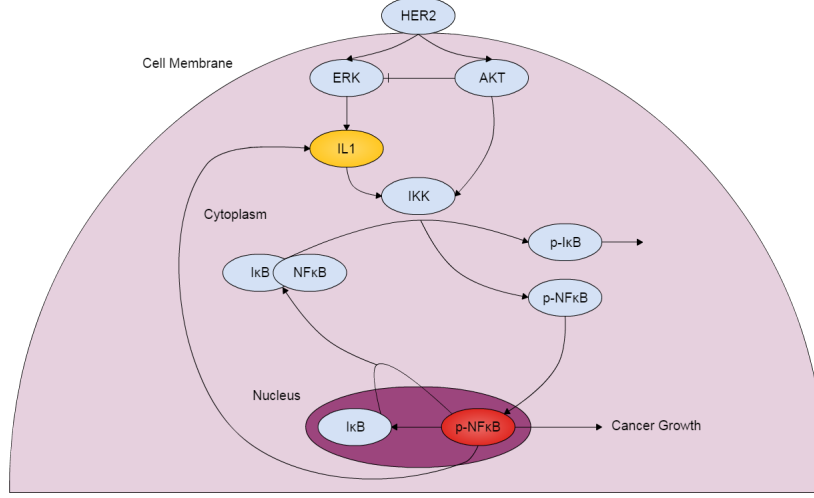


Figure 4.1: Schematic representation of the HER2 signaling pathway.

mass action kinetics, which states that the rate of a reaction is proportional to the concentration of the species involved in the reaction. The dynamics considered are activation, inhibition, dissociation, association, and degradation. There is an equation for each protein in the model that represents the rate of change of its concentration, resulting in the system of delay ordinary differential equations in (4.1) - (4.8), where the variables and parameters are listed in Tables 4.1 and 4.2, respectively.

$$\frac{dx_2}{dt} = k_1x_1 - k_2x_3x_2 - d_1x_2 \quad (4.1)$$

$$\frac{dx_3}{dt} = k_3x_1 - d_2x_3 \quad (4.2)$$

$$\frac{dx_4}{dt} = k_4x_2 + k_5x_8 - d_3x_4 \quad (4.3)$$

$$\frac{dx_5}{dt} = k_6x_3 + k_7x_4 - d_4x_5 \quad (4.4)$$

$$\frac{dx_6}{dt} = -k_8x_5x_6 + k_9x_9x_8 \quad (4.5)$$

$$\frac{dx_7}{dt} = k_8x_5x_6 - d_5x_7 \quad (4.6)$$

$$\frac{dx_8}{dt} = k_8x_5x_6 - k_9x_9x_8 \quad (4.7)$$

$$\frac{dx_9}{dt} = k_{10}x_8(t - \tau) - k_9x_9x_8 \quad (4.8)$$

$$\frac{dx_{10}}{dt} = x_6 + x_7 + x_9 \quad (4.9)$$

Table 4.1: Variables in the HER2 signaling pathway model.

Variable	Protein	Variable	Protein
x_1	[HER2]	x_6	[I κ B-NF κ B]
x_2	[ERK]	x_7	[p-I κ B]
x_3	[AKT]	x_8	[p-NF κ B]
x_4	[IL1]	x_9	[I κ B]
x_5	[IKK]	x_{10}	[I κ B] _{total}

Table 4.2: Parameters in the HER2 signaling pathway model.

Parameter	Description
k_1	[ERK] activation by [HER2]
k_2	[ERK] inhibition by [AKT]
k_3	[AKT] activation by [HER2]
k_4	[IL1] activation by [ERK]
k_5	[IL1] activation by [p-NF κ B]
k_6	[IKK] activation by [AKT]
k_7	[IKK] activation by [IL1]
k_8	[I κ B-NF κ B] phosphorylation by [IKK]
k_9	[I κ B-NF κ B] association from [I κ B] and [p-NF κ B]
k_{10}	[I κ B] synthesis by [p-NF κ B]
d_1	[ERK] degradation
d_2	[AKT] degradation
d_3	[IL1] degradation
d_4	[IKK] degradation
d_5	[p-I κ B] degradation

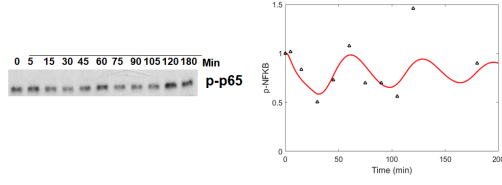
4.3 RESULTS

The concentrations of these proteins are measured in a cell culture at equilibrium at time zero. The western blots, quantified data, and model fits are in Figure 4.2. Each plot shows the relative change in NF κ B concentration versus time. The black symbol is the quantified western blot data, and the red line is the fitted model. In experiment a, HER2 is over-expressed. Then at time zero, HER2 is blocked, which causes NF κ B to initially decrease. NF κ B then increases and continues to oscillate damply near the

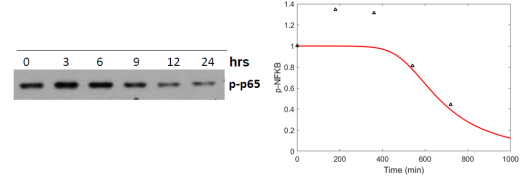
baseline level due to the delayed feedback loop with $I\kappa B$. Experiment b is the same as a, but with the data collected less frequently and for a long time, as a result of which we do not see oscillations. Here $NF\kappa B$ remains near the baseline level for about eight hours before it gradually decreases. In experiment c, HER2 is over-expressed. Then IL1 is added at time zero, which causes $NF\kappa B$ to increase significantly and then decrease. There is no HER2 in the cell culture in experiment d. At time zero IL1 is added, which causes $NF\kappa B$ to increase sharply and then gradually decrease. In experiment e, HER2 is over-expressed. Then IL1 is blocked at time zero, which causes $NF\kappa B$ to initially decrease sharply. It then oscillates dampedly. There is no HER2 in the cell culture in experiment f. At time zero IL1 is blocked, which causes $NF\kappa B$ to gradually decrease and then increase.

These results confirm that $NF\kappa B$ is downstream to HER2 since when HER2 is blocked, $NF\kappa B$ decreases. Inhibiting HER2 alone causes a gradual decay in $NF\kappa B$ after remaining near the baseline level for several hours. Additionally, these results show that IL1 activates $NF\kappa B$, even in the absence of HER2, since with and without HER2, addition of IL1 increases the $NF\kappa B$ concentration. Likewise, blocking IL1, with and without HER2, causes $NF\kappa B$ to decrease. Hence, since IL1 is upstream of $NF\kappa B$, it is a potential target for $NF\kappa B$ regulation as an effective strategy for tumor suppression in breast cancer therapy.

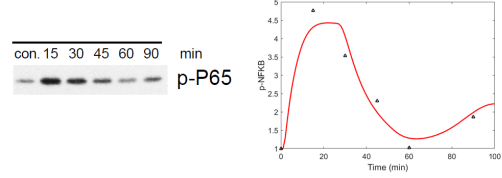
As seen in Figures 4.2 (a) and (b), after blocking HER2, $NF\kappa B$ concentration does not immediately decrease. For the short time data, there are damped oscillations around the baseline level for the first three hours. For the long time data, it remains near the baseline level for the first eight hours after which it gradually decreases. Therefore there is something upstream to $NF\kappa B$ that sustains it at a high level. Our model suggests IL1 is the intermediary in this pathway that sustains high $NF\kappa B$ concentration. And unlike with ERK or AKT, it is the positive feedback from $NF\kappa B$ to IL1 that creates this loop. In light of this, we predict the following scenario. As in



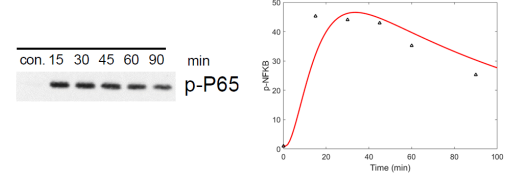
(a) Over-expression of HER2. Reach equilibrium. Block HER2.



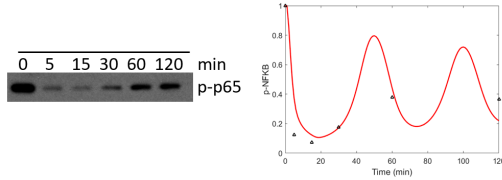
(b) Over-expression of HER2. Reach equilibrium. Block HER2.



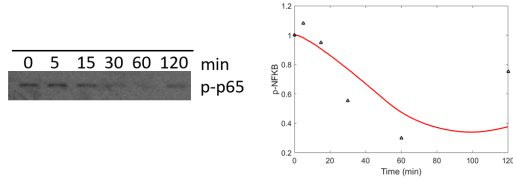
(c) Over-expression of HER2. Reach equilibrium. Add IL1.



(d) No HER2. Reach equilibrium. Add IL1.



(e) Over-expression of HER2. Reach equilibrium. Block IL1.



(f) No HER2. Reach equilibrium. Block IL1.

Figure 4.2: Western blot data, quantified data, and model fits of experiments.

Figure 4.2 (a), we over-express HER2 and let the system reach equilibrium. Then at time zero, we block the positive feedback from $\text{NF}\kappa\text{B}$ to IL1, parameter k_5 , in addition to HER2. The result is in Figure 4.3. We see that there is a sharp decrease in $\text{NF}\kappa\text{B}$ concentration, which shows that IL1 is what sustains high $\text{NF}\kappa\text{B}$ concentration in the absence of HER2.

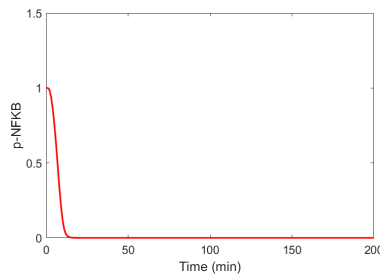


Figure 4.3: In silico prediction of over-expression of HER2. Reach equilibrium. Block HER2 and k_5 .

4.4 SIMULATION PROTOCOL

The model system of equations is solved numerically in MATLAB. The protein concentrations are normalized between 0 and 1. Over-expression of HER2 is simulated with a constant concentration of 1. The initial values of proteins are determined through optimization. The simulation is run until the system reaches equilibrium. Then at time zero the different experiments are simulated. The blot data is quantified. The data is then converted to relative change by dividing all values by the initial value. The model system of equations is first solved, and then converted to relative change.

All parameters and initial conditions are found using MATLAB's nonlinear constrained minimizer `fmincon`. Given a set of parameters and initial conditions, the system of delay ordinary differential equations is solved, after which the error sum of squares is calculated between the model output and the given data. This function is minimized in `fmincon` over the set of parameters and initial conditions. The experiments each have different sets of parameters which are found from minimization of the error sum of squares with their respective data. The range to search for the parameters and initial conditions is $[0, 1]$. The finite difference relative step size of `fmincon` is reduced to ensure proper exploration of the parameter space. The time delay is fixed between 15 – 60 minutes as a biologically reasonable range.

4.5 SENSITIVITY ANALYSIS

Sensitivity analysis is performed on the model to quantify how the model output varies with the parameter input. We perform global sensitivity analysis instead of local. Local sensitivity analysis only shows how model output varies with individual parameters. And it shows this variation at a point. Global sensitivity analysis, on the other hand, accounts for parameter interaction and shows how model output varies

with all parameters. And it shows this variation over the whole parameter space [66].

We use the variance based global sensitivity analysis method from Saltelli, *et al.* This method is model independent, has the capacity to capture the full range of variation of each parameter, and can indicate interaction effects among parameters. It is also computationally reasonable for our model. The variance based method quantifies how influential a parameter is on the model output. This gives us further understanding of the model dynamics by knowing which reactions are most influential. It also aids in the parameter fitting. Parameters that are influential can be prioritized, and parameters that are noninfluential can be fixed to a nominal value, thus reducing the dimension of the parameter space [66]. This may improve the parameter estimation since an optimizer's efficacy decreases with increasing number of unknowns.

Let k be the number of parameters, X_i be the i th parameter, and

$$Y = f(X_1, X_2, \dots, X_k)$$

be the model output. For $i = 1, 2, \dots, k$, we compute the first-order sensitivity indices,

$$S_i = \frac{V[E(Y | X_i)]}{V(Y)}, \quad (4.10)$$

and the total-effects sensitivity indices,

$$S_{Ti} = 1 - \frac{V[E(Y | \mathbf{X}_{\sim i})]}{V(Y)}, \quad (4.11)$$

where $E(\cdot | \cdot)$ and $V[\cdot]$ are the conditional expectation and variance, respectively, and $\mathbf{X}_{\sim i}$ indicates all parameters except X_i . S_i measures how influential X_i is. A large S_i means that X_i is influential. However, a small S_i does not mean that X_i is noninfluential. That is because X_i may be influential by interacting with other parameters. That is why we calculate S_{Ti} , which measures how influential X_i is while interacting with other parameters. A large S_{Ti} means that X_i is influential, and a small S_{Ti} means that X_i is noninfluential [66].

S_i and S_{Ti} are efficiently calculated by a Monte Carlo simulation as described in Saltelli, *et al.* [66, 67]. The $k = 15$ parameters are sampled $N = 2000$ times in two sets. All parameters are uniformly distributed in $[0, 1]$. The samples are quasi-randomly generated by Sobol's LP_τ sequence because this sequence is more uniformly distributed than pseudo-random samples generated by a computer [68]. This algorithm requires $N(k + 2)$ model evaluations.

The result of the sensitivity analysis on NF κ B concentration is given in Figure 4.4 (a). The sensitivity indices as a percentage are plotted versus each parameter in the model (4.1) - (4.8). We run the simulation by over-expressing HER2 and letting the system reach equilibrium. Then the first-order and total-effects sensitivity indices (4.10) and (4.11) are calculated at an equilibrium time point (800 minutes). We see that out of the 15 parameters, only five have a considerable influence on NF κ B concentration. Parameter number 8 is the most influential, which is an obvious result because it is the I κ B-NF κ B dissociation rate. What is not obvious is that parameter number 5, which is the activation rate for the positive feedback from NF κ B to IL1, is not influential. Knowing the most influential parameters allows us to reduce the dimension of the parameter space in studying the dynamics of NF κ B. In estimating parameters to fit data, we let the optimizer find the value of the five parameters, while setting the other ten to a nominal value. The identification of key parameters also aids in guiding what reactions to focus on in future lab and numerical experiments.

Since over-expression of HER2 is found in breast cancer patients, chemotherapy protocol includes drugs that block HER2. The problem is that in some patients, the tumor relapses despite receiving these drugs. NF κ B being both downstream to HER2 and able to cause cancer is of interest in this scenario. Therefore, in Figure 4.4 (b), we again compute the sensitivity indices (4.10) and (4.11) on NF κ B concentration in the model (4.1) - (4.8), but for the simulation over-expression of HER2, reach equilibrium, and then block HER2 at time 0. This is again calculated at an equilibrium value (800

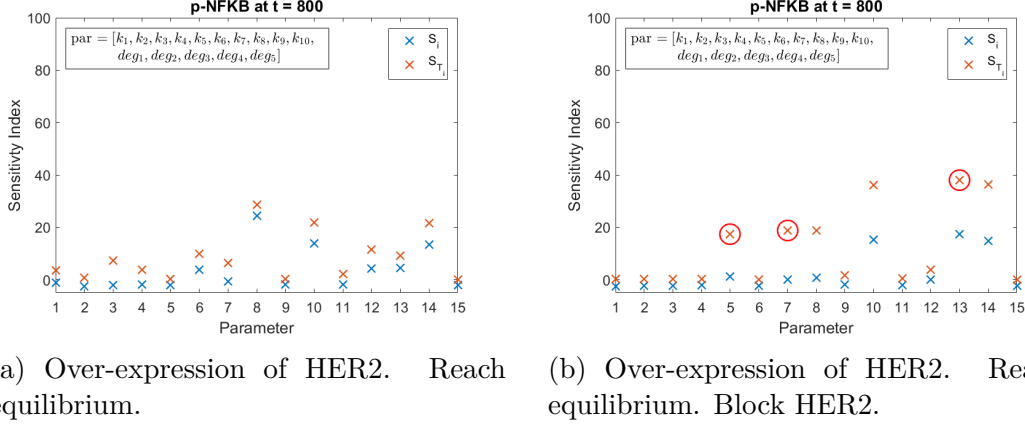


Figure 4.4: Sensitivity analysis of the model (4.1) - (4.8).

minutes after time 0). In this scenario versus the previous one, we observe is that the total-effects sensitivity index S_{T_i} greatly increases for parameters 5, 7, and 13 (circled in the figure). These parameters are the positive feedback from $\text{NF}\kappa\text{B}$ to IL1, the activation of IKK by IL1, and the degradation of IL1, respectively. This shows that in the absence of HER2, IL1 becomes increasingly important for $\text{NF}\kappa\text{B}$ regulation.

4.6 CONCLUSION

Over-expression of HER2 is found in breast cancer patients. The HER2 signaling pathway is critical in regulating CSC population in breast cancer tumors. Thus, breast cancer therapy includes drugs that block HER2. However many patients develop a resistance to these drugs, and their tumor relapses. Downstream of HER2 is $\text{NF}\kappa\text{B}$, whose aberrant regulation can cause cancer, making it a promising target for breast cancer therapy. In this study we discovered IL1's presence in this pathway. We developed a novel mathematical model of the HER2 signaling pathway that simplifies some of the reactions and accounts for the dynamics involving IL1. This simplified model is sufficient to reproduce experimental findings, and the presence of IL1 explains certain experimental observations. We made a prediction for a specific treatment scenario. And we performed global sensitivity analysis on the model to re-

veal the key parameters influencing $\text{NF}\kappa\text{B}$ concentration [64]. Our proposed pathway, model prediction, and sensitivity analysis suggest that IL1 is a crucial component in the HER2 signaling pathway for $\text{NF}\kappa\text{B}$ regulation and is thus a potential target for breast cancer treatment.

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